Chapter

Sellafield, Seascale, and Scandinavia: A Legacy of Radioactive Contamination with Future Implications for Gene Evolution in Affected Ecosystems

Chanda Siddoo-Atwal

Abstract

Radioactive waste from nuclear installations and nuclear reprocessing plants, nuclear accidents, and radioactive fallout from nuclear weapons testing constitute a serious problem facing future generations. Marine algae and phytoplanktons accumulate radionuclides from their surroundings and are used as bioindicators of radioactive pollution in the environment. In Northern Europe, the affected marine systems include the Irish Sea, the Baltic Sea, and the North Sea. The main sources of this radioactive contamination are global fallout from nuclear weapons tests, river transport from Siberia, and marine transport of discharges from Sellafield and Chernobyl. An increased leukemia incidence has been observed in young children at Seascale near Sellafield, and an elevated incidence of leukemia has been recorded among young people (0–24 years) in the French canton of Beaumont-Hague close to the Cap de la Hague nuclear reprocessing facility. In Scandinavia, scientists suspect that people in parts of Sweden are still dying from cancer caused by radiation from the Chernobyl accident. Moreover, the Baltic Sea is contaminated with man-made plutonium radionuclides from nuclear reprocessing. However, some experts are able to dismiss the above relationships due to important uncertainties over the estimation of radiation doses from environmental discharges based on a mutational theory of carcinogenesis. Consequently, it appears to be of paramount importance to reevaluate the current methods for cancer risk assessment in the case of radiation exposure within the context of an apoptotic model of carcinogenesis that could explain such a discrepancy. According to this new model, subtle differences in gene expression in response to a carcinogen can initiate cell death or apoptosis and act as a trigger for carcinogenesis. Simultaneously, future implications for human gene evolution are unavoidable.

Keywords: nuclear reprocessing, plutonium, leukemia, lung cancer, alpha- and gamma-radiation carcinogenesis

1. Introduction

Sellafield (UK) and Cap de la Hague (France) are the two largest centers for commercial reprocessing of nuclear fuel in the world. This process involves the

dissolution of spent fuel in boiling concentrated nitric acid, which results in the subsequent physicochemical separations of uranium and plutonium. Reprocessing operations release considerable volumes of liquid and gaseous wastes into the environment. These include large volumes of radioactivity, typically on a scale of several thousand more than that released by nuclear reactors.

1.1 Sellafield

In the case of Sellafield, aerial emissions have deposited two to three times the plutonium fallout from total atmospheric nuclear weapons testing within a 20-km radius of this facility. Since the inception of reprocessing at Sellafield in the 1960s, it has been estimated that between 250 and 500 kg of plutonium from the plant is now adsorbed onto sediments on the bed of the Irish Sea. Migration of these undersea deposits to coastal environments potentially represents a long-term hazard of unknown proportions [1].

The village of Seascale lies roughly south of Sellafield. A stretch of deserted beach runs northward toward the Sellafield plant, which has its discharge pipeline just 2 km off the coast. The beach used to be popular with bathers, but, now, many guide books make reference to the radioactive pollution from Sellafield. In fact, in 1993, a government survey found that the incidence of leukemia and non-Hodgkin's lymphoma was 14 times the national average and twice that in other areas of West Cumbria [2]. An increased incidence of retinoblastoma in children and a statistically significant increase in stillbirth risk in the Sellafield region have also been observed [1].

The main pathways for radiation exposure for people living in the vicinity of Sellafield are external radiation from airborne and deposited radionuclides, internal exposure resulting from inhalation of airborne radionuclides, and ingestion of radionuclides from contaminated food. In Sellafield, locally caught fish and shellfish have been found to be contaminated with toxic radionuclides, particularly, plutonium and americium [1].

1.2 Cap de la Hague

An elevated incidence of leukemia has been recorded among young people (0–24 years) in the French canton of Beaumont-Hague close to the Cap de la Hague nuclear reprocessing facility. In the latter case, two factors were found to be correlated strongly with increased leukemia risk: the use of local beaches for recreational activities by children and mothers during gestation and fish and shellfish consumption. In addition, a 3-year French epidemiological study in the region found a higher than expected morbidity in men from leukemia and respiratory cancers and leukemia and lung cancer in women [1].

1.3 Sea-to-land transfer

In Denmark, women have the highest rates of all forms of cancer in the Nordic countries [3], while their fish-eating neighbors in Norway have the highest rates of colorectal cancer for women in the world [4]. It is of some interest that Denmark, Ireland, and Norway have protested for many years over reprocessing at Sellafield and La Hague due to concern about the local impact on environment and health [1].

In parts of Sweden, scientists suspect that people are still dying from cancer caused by radiation from the Chernobyl accident [5]. Radioactive polonium, uranium, and plutonium have also been detected in the Baltic Sea where they are accumulated by various marine organisms. While the polonium and uranium

isotopes may be derived from natural geological sources, the principle sources of plutonium in the Baltic Sea are radioactive fallout from nuclear weapons testing, releases from nuclear power plants and nuclear processing facilities at Sellafield and Cap de la Hague, and radioactive debris originating from Chernobyl [6].

It has now been established that a potentially important pathway for radioactive discharges to humans involves sea-to-land transfer since significant quantities of radionuclides can become airborne in seaspray and be transported inland by the wind [7]. Thus, concerns over nuclear reprocessing have led to a number of studies examining the health risks that may be associated with such nuclide discharges and, ultimately, have resulted in a scientific report commissioned by the European Parliament [1].

1.4 Scientific and technological options assessment

The findings of this report suggest that the Sellafield facility (closed in 2018) was found to be in violation of several key European requirements. Marine discharges at Sellafield led to significant radionuclide concentrations in certain foodstuffs exceeding EC limits (and, in this case, the Irish fishwives' tales about mutant fish were very likely true) [8]. Radionuclide discharges to the Sellafield marine environment resulted in doses to critical groups exceeding ten times the current UK and three times the EU limits. Increases of key radionuclide releases from in the late 1990s and projected future releases from Sellafield were not in keeping with European standards or their UK obligations as a member state of the European Union (EU). Generally, radionuclide concentrations in the Cap de la Hague environment have decreased since the 1980s, and calculated doses from routine releases remain well within EU limits. However, past accidents at La Hague have led to population doses significantly exceeding EU limits and are estimated to be responsible for 36% of the leukemia risk level for the 0–24-year age category around the site.

Contaminated marine environments can result in radiation exposure and radionuclide accumulation by marine life from plants to fish, and transfer to larger organisms such as mammals can occur via the food chain. Short-term health effects on humans can include various cancers, notably leukemia, caused by changes in gene regulation, and thyroid disorders. Long-term health effects may include heritable genetic mutations transmissible to future generations. This could have a potentially negative impact on the human gene pool and human evolution in affected areas, especially with the loss of individuals with the least mutations [9]. Ultimately, this may affect the fitness of the species and lead to a major decline or genetic degradation of select human populations [10].

2. Local health effects

2.1 Epidemiology

The main radioactive contaminants in the immediate vicinity of the Sellafield nuclear reprocessing facility have been identified as plutonium [Pu] and americium [Am] as a result of soil core samples taken from 95 locations within a few kilometers of the Sellafield nuclear complex. High levels of Pu-239 and Pu-240 have been deposited within a few hundred meters of the site, declining to lower levels within 3 km. The activity ratio of these radioisotopes indicates that the plutonium originated from uranium of low irradiation suggesting that deposition occurred during the early years of plant operation. The presence of Am-241 also correlates strongly

with the Pu-239 and Pu-240 and is consistent with its derivation from Pu-241 deposition [11]. Pu-239 is formed by the spontaneous fission of U-238, which is a by-product of the uranium enrichment process routinely carried out at nuclear power plants [12].

In 1983, a cluster of cancers, most readily produced by ionizing radiation, were discovered in Seascale, a village situated 3 km from Sellafield, which is the principal nuclear reprocessing plant in the UK. It involved the occurrence of non-Hodgkin's lymphoma (NHL) with lymphoblastic leukemia in young people under the age of 25, who lived in Seascale in the period between 1955 and 1983 [13]. A subsequent scientific study confirmed that there was a marked excess of acute lymphatic leukemia (ALL) in Seascale [14]. In 1986, an excess of acute lymphatic leukemia was discovered near Dounreay, the site of the only other nuclear reprocessing plant in the UK [15]. Finally, in 1993, when an excess of acute lymphatic leukemia was also recorded in Egremont, a small town 7 km north of Sellafield, the emerging epidemiological pattern could no longer be ignored [14]. In fact, the incidence rates of ALL and NHL were increased to a similar extent in Seascale when the parents were incomers from other parts of the country or locals suggesting an environmental component to the problem [16]. Moreover, a significant excess of these cancers has continued to be observed in Seascale since this data was first collected.

Interestingly, one study measured the concentrations of Pu-239 and Pu-240 in the teeth of children throughout Great Britain and Ireland. Regression analysis showed that the concentrations of plutonium decreased with increasing distance from the Sellafield facility and suggests that this plant is not only a source of radioactive contamination locally, but it may affect a wider population within the British Isles [17]. An earlier study noted similar differences for plutonium levels in bone collected from people living in West Cumbria as compared with those living at sites remote from this location in the UK [18].

Further studies were commissioned by the Irish State to examine the possible effects of nuclear pollution from Sellafield on the coast of Ireland. The results showed a seacoast effect in coastal areas close to North Wales, particularly in towns where there was intertidal sediment contaminated with radioactive material from Sellafield or other historical sources. This was evidenced as a sharp rise in risk for leukemia in children and adults, especially near the northern entrance of the Menai Strait, which has fine intertidal sediment significantly contaminated with plutonium and other radioactive materials from Sellafield [19]. A follow-up localized these disturbing results in Caernarfon, Gwynedd, and Anglesey [20]. The explanation given was that sea-to-land transfer of radioactive particles followed by inhalation represented a risk to those living in the 0–1 km coastal strip since the particles could be transferred from the lungs to the lymphatic system resulting in leukemia. Such observations only serve to highlight the painful fact that acute uncertainties exist in the dosimetry of primary alpha-emitters, such as plutonium, in children and the fetus [21].

In autopsy tissues from west Cumbrian workers who had been employed in the nuclear energy industries, plutonium concentrations have been found to be generally higher than tissue concentrations in people from other regions of Great Britain. Furthermore, isotopic analysis using mass spectrometry has provided some evidence that this plutonium originated from aerial discharges from the British Nuclear Fuels Plant at Sellafield [22].

In radiation workers from the Sellafield plant, a significant excess of deaths has been recorded from cancer of the pleura and thyroid. In addition, a positive correlation has been observed between accumulated external radiation dose and mortality from leukemia, multiple myeloma, and all lymphatic and hematopoietic cancers.

There were also significant increases in risk with cumulative plutonium plus external radiation doses for all lymphatic and hematopoietic neoplasms. As a result, it has been concluded that the cancer incidence in Sellafield employees exposed to plutonium was significantly increased as compared with other radiation workers [23]. Furthermore, in a pooled cohort analysis of Sellafield (UK) and Mayak (Russia) workers, lung cancer risk from occupational plutonium exposure was studied. Poisson regression models provided a clear evidence of a linear association between cumulative internal plutonium lung dose and risk of lung cancer incidence and mortality in the pooled cohort [24].

2.2 Animal studies

Studies in animals have demonstrated that exposure to relatively large doses of plutonium (as compared with human doses) can cause tumors in the tissues in which it is retained [25].

As early as 1959, a single inhalation exposure to a smoke of plutonium oxide in rats was correlated with characteristic pathologic changes in the lungs at the sites where the material was deposited using autoradiographic and histopathologic methods. Moreover, the malignant tumors which occurred in many of the animals could be related to this severe focal damage in the lungs as a result of the plutonium oxide exposure [26]. It has also been recorded that a single intraperitoneal injection of monomeric Pu-239 in mice results in a significantly higher incidence of bone cancer in females than males, while castration of males equalizes the frequency of bone sarcomas in both sexes [27]. In another study, the cancer risk posed by Pu-239 was reduced in adult female mice by chelation therapy with subcutaneous injections of Zn Na_3 diethylenetriaminepentaacetate (Zn-DTPA) [28]. More recently, it was demonstrated that catechol-3, 6-bis(methyleiminodiacetic acid) (CBMIDA) is as effective as Zn-DTPA and Ca-DTPA in removing plutonium from the liver of rats and superior to both Zn-DTPA and Ca-DTPA in removing plutonium from bone [29].

Another significant study with rats found that point mutations in the p53 (or Tp53) tumor suppressor gene, which is involved in mediating apoptosis, seem to play a role in the development of lung tumors following inhalation exposure to plutonium dioxide [30]. However, these base transitions are not associated with nuclear accumulation of p53 protein suggesting that this may represent a later step in carcinogenesis involving resistance to apoptosis and cell transformation. Mutations in this gene are often encountered in lung tumors from uranium miners, and p53 appears to play a critical role in the cellular response to genetic damage caused by radiation in humans [31]. In addition, epigenetic inactivation of the p16 gene by methylation is common in rat lung tumors induced by Pu-239. The prevalence of p16 methylation in lung adenocarcinoma samples collected from Mayak plutonium workers is also significantly increased as compared with controls. The p16 protein has been reported to regulate apoptosis in diverse cell types [32].

The experimental inhalation of plutonium dioxide aerosols by beagle dogs revealed the long-term retention of plutonium in the lungs. Approximately 9% of the alveolar plutonium deposits were transferred to hilar lymph nodes by the first year and started to be detectable in abdominal lymph nodes about 2 years after inhalation [33]. More recent studies provide evidence that lung neoplasms can be induced in dogs by Pu-239 and can be associated with the expression of epidermal growth factor receptor [EGF-R] as in human lung tumors [34].

Furthermore, beagle dogs exposed to plutonium-nitrate and subjected to its retention in their tissues have been diagnosed with tumors in bronchioloalveolar,

peripheral, and subpleural alveolar regions of the lung. The TUNEL assay revealed an elevation of apoptosis in the tracheal mucosa, tumor cells, and nuclear debris in the alveoli and lymph nodes of the beagles with statistically significant modifications in Fas ligand, B-cell lymphoma 2, and caspase-3 expression. It is of note that a comparably exposed human subject in the same study did not develop pulmonary tumors or display an elevated rate of apoptosis in lung tissues [35].

2.3 Cell culture studies

Cell studies on peripheral blood lymphocytes from workers with significant plutonium body burdens have revealed an increase in chromosome aberrations. Radiation-induced breakpoints were randomly distributed among the chromosomes according to length. However, the distribution of the breakpoints within the chromosomes displayed an excess in the centromeres and telomeres. This study suggests that plutonium depositions within the body can cause such aberrations since external radiation exposure was taken into account [36]. A further follow-up study performed on Sellafield workers with 20–50% and >50% maximum permissible body burdens (MPBB) of plutonium confirmed that these results are consistent with the hypothesis that hematopoietic precursor cells are being irradiated by internally deposited plutonium with subsequent selection resulting in only those cells with symmetrical aberrations reaching the peripheral lymphocyte pool [37]. Presumably, elimination of the nonviable cells occurs via programmed cell death or apoptotic pathways.

B lymphocyte precursor cells, which are the target cells for acute lymphoblastic leukemia in children, are highly susceptible to the lethal effects of α-particles and have a very low probability of surviving a single α-track [38]. Subsequently, alpha-irradiation has been reported to cause transmissible chromosomal instability, characterized by non-clonal cytogenetic aberrations with a high frequency of chromatid-type aberrations and a lower frequency of chromosome-type aberrations, in the clonal descendants of human hematopoietic stem cells. Delayed apoptotic cell death is evident in these clonal populations [39]. Furthermore, an interesting study demonstrated that both high-LET fast neutrons (of the type emitted by plutonium-239) and low-LET 60Co gamma rays induce apoptosis independently in resting human peripheral blood lymphocytes. Dose-response curves for each of these two types of radiation are characterized by an initial steep increase in the number of apoptotic cells below 1 Gy and a flattening of the curves at higher doses toward 5 Gy [40].

Apoptosis can also be selectively induced in transformed cells by neighboring normal cells via cytokine and reactive oxygen species (ROS)/reactive nitrogen species (RNS) signaling. In fact, in rat fibroblasts, high-LET α-particles are more effective than low-LET X-rays in stimulating intercellular induction of apoptosis for any given irradiated fraction of cells at very low doses. The increase in intercellular induction of apoptosis results from nitric oxide free radical (NO*) and peroxidase signaling mediated by transforming growth factor beta [TGF-β] [41]. In human fibroblasts following exposure to 0.1 and 1 Gy α-particles, irradiated populations display a dose-dependent increase in chromosome-type aberrations at the first cell division. Nonirradiated neighbor (bystander) fibroblast populations also demonstrate elevated chromatid-type aberrations. Both irradiated and bystander populations have significantly higher frequencies of chromatid aberrations over 25 doublings than controls [42]. These results support the increasing evidence that the biological effects of ionizing radiation are not limited to irradiated cells, but can extend to nonirradiated neighbors and be seen as genomic instability in their progeny at subsequent generations.

In another intriguing study, it was shown that human papillomavirus-immortalized human bronchial epithelial (BEP2D) cells can undergo malignant transformation when exposed to 1.5 Gy of α-particles emitted by a Pu-238 source [43]. A non-tumorigenic human thyroid epithelial cell line (HTori-3) has also been transformed into tumorigenic cells by exposure to alpha particles in vitro. These tumor cells were screened and found to contain experimentally induced mutations in the p53 tumor suppressor gene generated by irradiation of the human thyroid epithelial cell line [44].

3. Long distance ecosystem effects

3.1 Measurement of plutonium in sea water

Plutonium in the Baltic Sea has been assessed in precipitation, water, sediments, and microalgae. The major source of plutonium is fallout from nuclear tests, while European reprocessing facilities have contributed significant quantities of all plutonium isotopes. The Chernobyl accident contributed very little to overall plutonium concentrations of Pu-239 and Pu-240, whereas the Pu-238 and Pu-241 contributions were more significant [45]. Significantly increased concentrations of plutonium have also been found in the subsurface layers of the Norwegian and Greenland Seas. The plutonium activity ratio [^{238}Pu/^{239,240}Pu] found in both peaks displays a significant influence of Sellafield discharges [46]. Measurements of isotopic atomic ratios of plutonium in bottom deposit samples from the Norwegian and Greenland Seas show that the contribution of α activity of industrial plutonium from the European reprocessing plants, mainly Sellafield, on the background of global fallouts is 20–50% of total α activity (Pu-238-240) and 70–95% of total β activity (Pu-241) [47]. Moreover, a transfer factor for both conservative and non-conservative (including plutonium) Sellafield discharges has been detected in East Greenland Current Polar Water, a water mass which reflects contaminant levels in Arctic Ocean surface water [48].

3.2 Measurement of plutonium in plants

An interesting study analyzing Swedish lichen samples from various parts of Sweden demonstrated that in the areas most contaminated by the Chernobyl accident, the plutonium contributions from Chernobyl were as high as 85%. Sellafield-derived neptunium (Np) was found in brown seaweed samples from the west coast of Sweden 4–5 years after discharge (1995–1996), suggesting that it has greater mobility than plutonium in this particular marine environment [49]. Furthermore, the long-lived anthropogenic radionuclides Np-237, Pu-239, and Pu-240 were determined in marine environmental samples (seaweed and seawater) from Swedish-Danish waters and the North Atlantic Ocean at various locations. Most of the Np-237 in these waters is considered to originate from the Sellafield plant with some contribution from global fallout. There was quite a wide variation in Np-237 activity concentrations in *Fucus vesiculosus* and Pu-240/Pu-239 atomic ratios in *F. vesiculosus* samples [50]. In Norway, *F. vesiculosus* samples collected in the North Sea, Skagerrak, and in selected fjords also contain Pu-239 and Pu-240 concentrations with relatively large fluctuations from year to year with a slowly decreasing trend in the activity concentrations from 1980 to 2010, possibly coinciding with declining Cap de la Hague emissions. However, seawater samples collected in the North Sea near Scotland do not display a similar decreasing trend in Pu-239 and Pu-240 radioactivity, thereby suggesting a Sellafield effect [51].

3.3 Measurement of plutonium in marine biota

Plutonium-239 and plutonium-240 concentrations in Baltic biota have revealed that these radionuclides are strongly accumulated by some species such as algae, benthic animals, and fish [52]. In the southern Baltic Sea, the Pu-239 and Pu-240 concentrations in surface seawater samples range from 5.2 mBq m^{-3} for Gdańsk Bay to 150 mBq m^{-3} for Pomeranian Bay, and plutonium has been found to be distributed in parts of cod gills and skin [53]. At the same time, it is important to note that the major fraction of plutonium in the Baltic Sea is rapidly associated with sediments and only 1% is present in the water column. Therefore, in view of the above findings, it is of the utmost importance to identify safe scavenging processes and filtration techniques for future remediation efforts [45]. Some of the remediation strategies previously adopted for surface waters affected by the Chernobyl accident include adding chemicals to bind radionuclides, construction of traps to contain contaminated sediments, and dredging of contaminated deposits [54].

4. Possible mechanisms of alpha- and gamma-radiation carcinogenesis

4.1 An apoptotic model of carcinogenesis

Classically, experimental carcinogenesis is a complex, multistage process including initiation, promotion, and malignant progression in which the failure of DNA repair mechanisms and the subsequent clonal expansion of damaged cells play a pivotal role. However, more recently, it has become apparent that the pathogenesis of cancer is closely connected with aberrantly regulated apoptotic cell death and the resulting deregulation of cell proliferation [55, 56].

The Ames assay as a universal test for carcinogenicity was based on the classical model of carcinogenesis involving the failure of DNA repair mechanisms and the subsequent clonal expansion of mutated cells. However, mutagenicity in bacterial strains is not always an indicator of carcinogenicity since many carcinogens are not mutagenic [57]. Although this may be one feasible mechanism of carcinogenesis in laboratory models, it does not adequately fit many existing systems of carcinogenesis which are increasingly connected with the dysregulation of apoptotic mechanisms in the cell.

Somatic cell and germline point mutations do occur, and the frequency of mutation can be accelerated by external factors like mutagenic substances such as ionizing radiation. Spontaneously, this is still considered to be a relatively slow process and, probabilistically, more likely to have an effect on a later step of carcinogenesis involving cell immortalization or transformation than to initiate carcinogenesis, or, more likely, even to affect future generations. According to Darwinian doctrine, random mutations in the general population result in the gradual evolution of a species. With exposure to mutagens in the environment, though, this genetic evolution can be sped up resulting in the acquisition of new traits or characteristics by a particular group. Ultimately, there is always the possibility that this unnaturally accelerated evolution may negatively impact the fitness of the species.

In the two-stage model of tumor formation (**Figure 1**), step I exposure to a carcinogen, possibly facilitated by a genetic predisposition, results in an epigenetic or genetic event causing continuous apoptotic activation of cells in the target tissue. In step II, when the carcinogen may or may not be present, resistance to apoptosis and continuous cell proliferation result due to another genetic or epigenetic event.

The extended proliferation of these somatic cells can result in the development of the neoplastic phenotype [58]. According to this model based on human skin carcinogenesis, while an epigenetic change is more likely to occur in the first step of carcinogenesis, a genetic mutation is more likely to occur in the second step of carcinogenesis as a function of probability [59]. A nice example is provided by the p53 mutations which appear to inhibit cell death in mammalian lung tumors induced by plutonium dioxide.

4.2 Alpha- and gamma-radiation-induced apoptosis

It is well known that radioactive metals and their isotopes routinely have long half-lives and many emit gamma radiation. As an example, the half-life of uranium-238 [U-238] is 4.46 billion years, while that of U-235 is 704 million years, and, although they are primarily alpha-emitters, both also emit gamma radiation. In addition, some plutonium radioisotopes with intermediate half-lives (up to thousands of years) emit gamma rays along with alpha and beta particles [60]. Thus, the potential health effects on wildlife and humans are virtually unlimited in terms

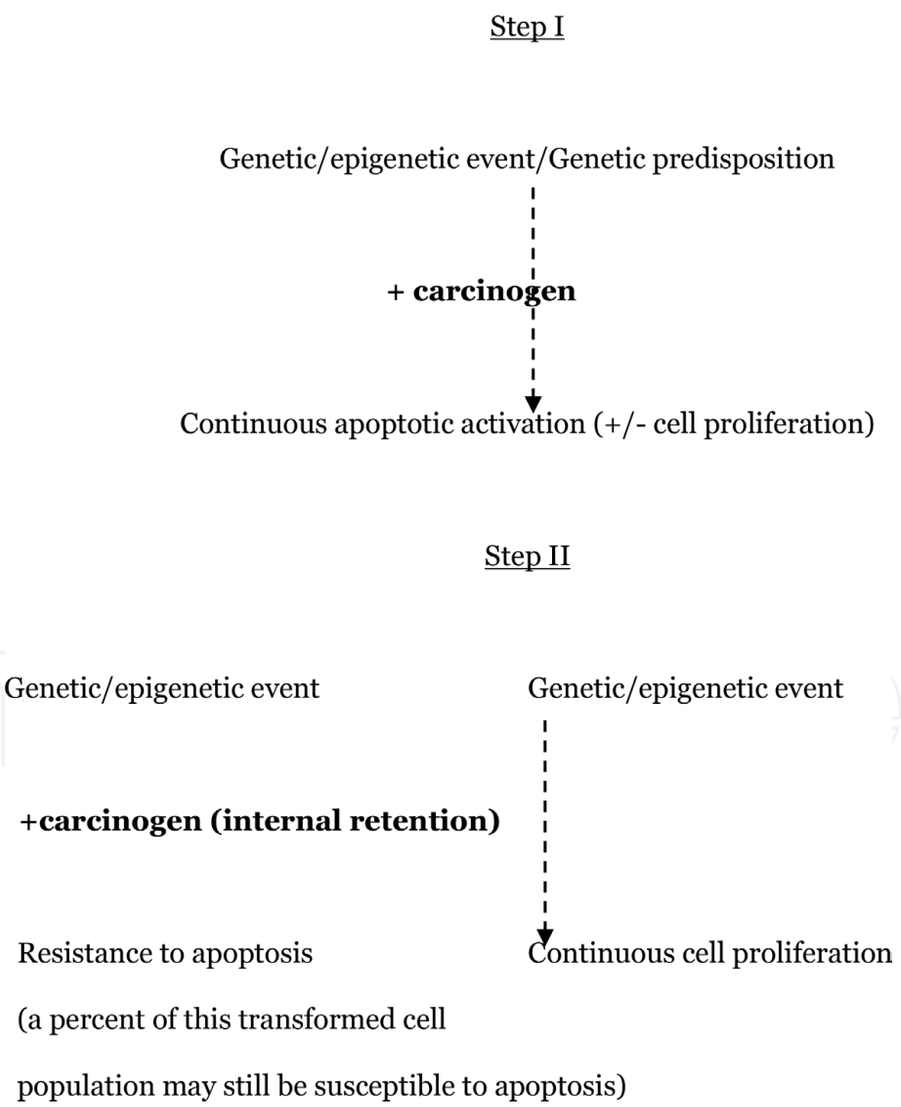

Figure 1.
Two-stage model of tumor formation. Step I exposure to a carcinogen, possibly facilitated by a genetic predisposition, results in an epigenetic or genetic event causing continuous apoptotic activation of cells in the target tissue. In step II, when the carcinogen may or may not be present, resistance to apoptosis and continuous cell proliferation result due to another genetic or epigenetic event.

of duration once the environment becomes contaminated with significant levels of such radioisotopes due to nuclear accidents or nuclear reprocessing activities.

Alpha-irradiation has been reported to cause delayed apoptotic cell death in the clonal descendants of human hematopoietic stem cells. Another study has demonstrated that high-LET fast neutrons (of the type emitted by plutonium-239) induce apoptosis in resting human peripheral blood lymphocytes. Apoptosis can also be selectively induced in transformed mammalian cells by neighboring normal cells in response to high-LET α-particles via cytokine and reactive oxygen species (ROS)/reactive nitrogen species (RNS) signaling.

Like UV-rays, ϒ-rays are considered to be a complete carcinogen. In one large study, 400 days (a little over 1 year) of continuous external ϒ-ray exposure induced tumors in a significant percentage of treated mice (>86.7%) and resulted in their premature deaths [61]. External exposure to ϒ-rays has been reported to stimulate apoptosis in certain cell types including rat thymocytes, mouse myeloid cells, and human lymphoid cells. Lymphoblastoid cell lines derived from healthy individuals undergo p53-independent apoptosis in response to high-LET radiation and p53-dependent apoptosis in response to low-LET radiation [62]. Furthermore, some human carcinoma cell lines exposed to internal ϒ-radiation via the decay of a DNA-incorporated radionuclide [I-125] display radiosensitivity as a result of activation of apoptotic pathways [63]. Thus, exposure to both external and internal ϒ-radiation sources can stimulate apoptotic cell death.

4.3 Uranium and apoptotic pathways

It appears that different isotopic compositions of uranium like many other heavy metals can penetrate to the subcellular level resulting in bioaccumulation and initiation of oxidative stress in zebrafish tissues [64]. At subtoxic concentrations (>100 μM), depleted uranium precipitates mainly in the nucleus of the human kidney, liver, and neuronal cell lines [65]. Chemically, uranium can activate oxygen species in the course of redox reactions via the redox chemistry of transition metals [66] and enhance free radical production via the ionization phenomenon induced by alpha particle emissions to produce DNA damage in the form of double-strand breaks [67, 68]. Although uranium can emit alpha, beta, and gamma radiation, alpha particle emissions are of the greatest relevance in relation to depleted uranium, which is a waste product of uranium enrichment [69]. Thus, uranium is capable of initiating chemotoxicity and radiotoxicity [70] via the generation of free oxygen species and possibly via more direct mechanisms involving DNA damage in cells. Both biochemical pathways can stimulate cell death or apoptosis, which has been linked to carcinogenesis in various cancer models. In fact, the loss of equilibrium between cell death and cell proliferation in a tissue may play a critical role in tumor formation (**Figure 1**) [71, 72].

4.4 Plutonium and apoptotic pathways

Plutonium is mainly deposited in the human lungs, liver, and skeleton, where it is retained for many years. Pu-239 has a physical half-life of 24, 110 years and a biological half-life of 20–50 years [73]. Intravascular administration of plutonium citrate in the human body results in radioactive concentration in the bone marrow, the liver, the bone, the spleen, the kidney, and the lungs [74]. Environmental transfer is determined by its solubility in human body fluids such as its measurement via urine bioassays [25]. This environmental plutonium transfer can give rise to α-particle radiation doses of ≈3–7 μSv/a in human bone and ≈10–20 μSv/a

in the liver [12], which may result in chemo- and radiotoxicity via the ionization phenomenon induced by alpha particle emissions similar to that caused by depleted uranium. Previously, the incidence of multiple primary cancers in Nagasaki plutonium atomic bomb survivors has been associated with radiation exposure [75]. Interestingly, recent autoradiographic analysis of paraffin-embedded tissue samples from Nagasaki atomic bomb victims (who died within 5 months after the bombing) has confirmed the presence of alpha-tracks from deposited plutonium, and, so, the contribution of internal plutonium radiation exposure [Pu-239] to overall toxicity cannot be dismissed [76]. Thus, a two-stage model of tumor formation in the case of plutonium is plausible, possibly with a degree of apoptosis occurring in the transformed cell population due to continued exposure to the internalized plutonium (**Figure 2**).

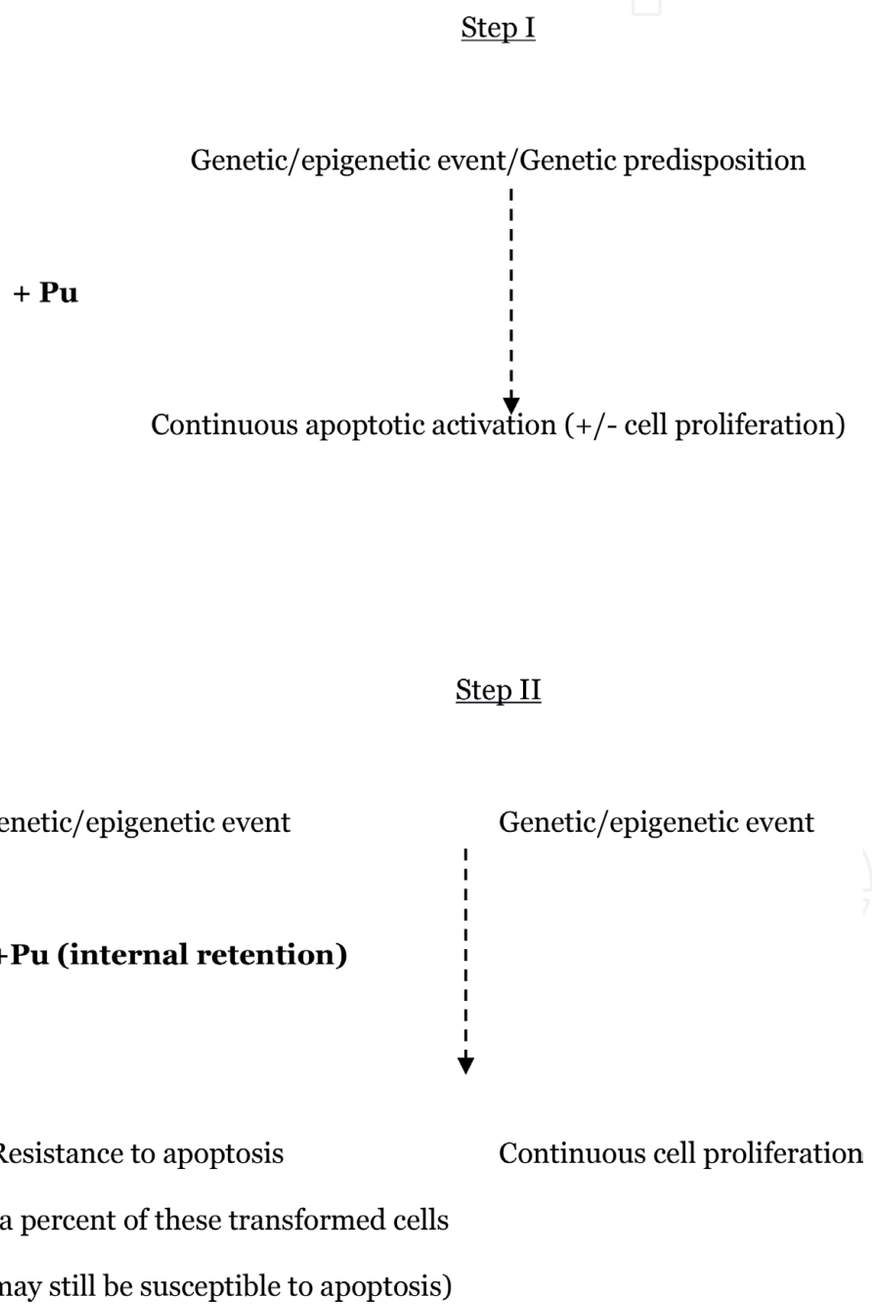

Figure 2.
Two-stage model of tumor formation for plutonium. A two-stage model of tumor formation in the case of plutonium is plausible, possibly with a degree of apoptosis occurring in the transformed cell population due to continued exposure to the internalized plutonium.

5. Discussion

Epidemiological studies in the north of England revealed a cluster of cancers most readily produced by ionizing radiation in three villages situated close to nuclear reprocessing plants. When an elevated incidence of acute lymphatic leukemia was observed in children living in all three locations, the emerging pattern could no longer be ignored. Subsequently, the deposition of radioactive plutonium was found in the immediate vicinity of the Sellafield plant, and locally caught fish and shellfish were found to be contaminated with toxic radionuclides, particularly, plutonium. A study that measured the concentration of plutonium in the teeth of children in Great Britain and Ireland concluded that it decreased with increasing distance from the Sellafield facility and suggested that this plant was not only a source of radioactive contamination locally, but that it may be affecting a wider population within the British Isles. Further studies commissioned by the Irish State found a sharp rise in the risk for leukemia in children and adults, especially near the northern entrance of the Menai Strait, which has fine intertidal sediment significantly contaminated with plutonium and other radioactive materials from Sellafield due to the sea-to-land transfer of radioactive particles. Plutonium concentrations in west Cumbrian workers from the nuclear energy industries were generally higher at autopsy than tissue concentrations in people from other regions of Great Britain, and isotopic analysis confirmed that this plutonium originated from aerial discharges from the British Nuclear Fuels Plant at Sellafield. In fact, the cancer incidence in Sellafield employees exposed to plutonium was significantly increased as compared with other radiation workers. A positive correlation was observed between accumulated external radiation dose and mortality from leukemia, multiple myeloma, and all lymphatic and hematopoietic cancers. There were also significant increases in risk with cumulative plutonium plus external radiation doses for all lymphatic and hematopoietic neoplasms. Moreover, a combined study between Sellafield and Mayak nuclear reprocessing plants found evidence of a linear association between cumulative internal plutonium lung dose and risk of lung cancer incidence.

Animal studies in rats revealed that a single inhalation of plutonium oxide smoke can result in malignant tumors of the lungs. A single intraperitoneal injection of plutonium-239 in mice particularly predisposes females to bone cancer. Plutonium dioxide inhalation in rats is associated with lung tumors displaying point mutations in the p53 tumor suppressor gene. Mutations in p53 are found in lung tumors from uranium miners, as well, suggesting a similar mechanism of carcinogenesis. Inactivation of the p16 gene by methylation is common in rat lung tumors induced by Pu-239. Methylation of p16 is also observed in lung adenocarcinomas from Mayak plutonium workers. Lung neoplasms can be induced in beagle dogs by Pu-239 and can be associated with the expression of epidermal growth factor receptor [EGF-R] as in human lung tumors. Furthermore, beagle dogs exposed to plutonium-nitrate have been diagnosed with tumors in bronchioloalveolar, peripheral, and subpleural alveolar regions of the lung.

Chromosome studies with peripheral blood lymphocytes from plutonium workers may provide indirect evidence that hematopoietic precursor cells are being irradiated by internally deposited plutonium with subsequent selection and elimination of badly damaged cells via apoptosis. B lymphocyte precursor cells are highly susceptible to the lethal effects of α-particles, and high-LET fast neutrons (of the type emitted by plutonium-239) induce apoptosis in resting human peripheral blood lymphocytes. Delayed apoptotic cell death is evident in clonal descendants of human hematopoietic stem cells exposed to alpha-irradiation. Apoptosis can also be

selectively induced in transformed rat fibroblasts by neighboring normal cells via cytokine and reactive oxygen species (ROS)/reactive nitrogen species (RNS) signaling. It has been shown that human papillomavirus-immortalized human bronchial epithelial (BEP2D) cells can undergo malignant transformation when exposed to 1.5 Gy of α-particles emitted by a Pu-238 source.

6. Conclusions

Thus, according to a new method for cancer risk assessment based on an apoptotic model of carcinogenesis, there is sufficient evidence to support that plutonium is a carcinogen associated with the etiology of leukemia and lung cancer in humans, especially when it is internalized from the environment. Comparative apoptosis studies in normal bronchial epithelial cells exposed independently to α-particles from a Pu-239 source and plutonium citrate might be useful in exploring the differing effects of external and internal alpha-irradiation.

In addition, recent results from many laboratories show that chromosomal instability in proliferating mammalian cells is characterized by a persistent increase of chromosomal aberrations and rearrangements occurring de novo during successive cell generations. This phenotype can be induced equally by low- and high-LET irradiation in lymphocytes at very low doses of exposure, conceivably contributing to cancer risk [42, 77]. The potential future implications in select human groups living in environments contaminated with radioactive substances are staggering and may include ailing populations with the elimination of fit individuals from the gene pool due to persistent illness or disease.

Moreover, the possibility of detecting the biological effects of Sellafield radioactive contamination as far afield as Scandinavia is a distinct reality since significant quantities of radionuclides can become airborne in seaspray and be transported inland by the wind for long distances. Plutonium from the Sellafield plant has been identified in coastal areas of North Wales where it has been correlated with an increased risk for leukemia. It has also been detected in the Baltic Sea, the Norwegian and Greenland Seas, and in seawater and seaweed collected from Swedish-Danish waters. Furthermore, plutonium-239 and plutonium-240 have been found in the gills and skin of cod from the Baltic Sea. Therefore, combined radiation risks including a Sellafield contribution may be elevating cancer rates in Scandinavian populations.

In this day and age of increasingly widespread radioactive pollution, heavy metal chelation therapy is an essential addition to all modern hospitals. As an example, injections of a chelation agent, Zn-DTPA, have been found to be useful for plutonium detoxification and reducing the plutonium-associated cancer risk in female mice. Although the biochemical pathways for plutonium detoxification in the human body are not well understood, free radicals are eliminated via various antioxidant activities including enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione S-transferase. Zinc supplementation has also been reported to be potentially beneficial in ameliorating the health hazards of nuclear waste such as depleted uranium, which may generate free radicals as a result of similar cellular mechanisms to plutonium. Thus, zinc absorption via the regular use of zinc oxide-based sunscreens may provide some protection against certain heavy metal environmental pollutants [78, 79].

Finally, this grave environmental issue begs the question of moral culpability and social responsibility. Therefore, it is suggested that radionuclide remediation [79] should be practiced and promoted by violators of international nuclear safety

regulations, Sellafield in this particular case. Compensation should be meted out to the injured parties in the case of nuclear accidents at Sellafield and Cap de la Hague. Finally, the frequency of accidents and future costs of such negligence at nuclear and reprocessing installations including the possible decimation of the species should be weighed carefully by countries when considering the attractive attributes of alternative clean energy sources like wind, water, and solar power. Once nuclear power plants start springing up around the world and producing vast quantities of radioactive waste, there will be no way of turning back the clock and decontaminating the planet.

Author details

Chanda Siddoo-Atwal
Moondust Cosmetics Ltd., West Vancouver, Canada

*Address all correspondence to: moondustcosmetics@gmail.com

References

[1] Schneider M, Coeytaux X, Faïd YB, Marignac Y, Rouy E. Possible toxic effects from the nuclear reprocessing plants at Sellafield and Cap de la Hague. European Parliament. STOA Scientific and Technological Options Assessment. 2001:1-168

[2] 1999-2019, Core, Cumbrians Opposed to a Radioactive Environment. Available from: http://corecumbria.co.uk

[3] Denmark still worst country in the Nordics for cancer. The Local. 2017. Available from: www.thelocal.dk

[4] Bazilchuk N. Cancer mystery in Norway. ScienceNordic. 2017. Available from: http://sciencenordic.com

[5] Abdelrahman R. Swedes still dying from Chernobyl radiation. The Local. 2007. Available from: www.thelocal.se

[6] Skwarzec B. Polonium, uranium and plutonium in the Southern Baltic Sea. AMBIO. 1997;**26**(2):113-117

[7] McKay WA, Pattenden NJ. The transfer of radionuclides from sea to land via the air a review. Journal of Environmental Radioactivity. 1990;**12**:49-77

[8] Martin J. Ireland could sue British operators over contamination. The Irish Post. 2014. Available from: www.irishpost.com

[9] Muller HJ. The relation of recombination to mutational advance. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 1964;**1**(1):2-9. DOI: 10.1016/0027-5107(64)90047-8

[10] Loewe L, Hill WG. The population genetics of mutations: Good, bad and indifferent. Philosophical transactions of the Royal Society of London. Series B, Biological Sciences. 2010;**365**(1544):1153-1167. DOI: 10.1098/rstb.2009.0317

[11] Jones SR, Willans SM, Smith AD, Cawse PA, Baker SJ. Deposition of actinides in the vicinity of Sellafield, Cumbria: Accounting for historical discharges to atmosphere from the plant. Science of the Total Environment. 1996;**183**(3):213-229. DOI: 10.1016/0048-9697(96)05067-X

[12] Taylor DM. Environmental plutonium in humans. Applied Radiation and Isotopes. 1995;**46**(11):1245-1252. DOI: 10.1016/0969-8043(95)00167-C

[13] Doll R. The Seascale cluster: A probable explanation. British Journal of Cancer. 1999;**81**(1):3-5

[14] Craft AW, Parker L, Openshaw S, Charlton M, Newell J, Birch JM, et al. Cancer in young people in the north of England, 1968-85: Analysis by census wards. Journal of Epidemiology and Community Health. 1993;**47**(2):109-115

[15] Heasman MA, Kemp IW, Urquhart JD, Black R. Childhood leukemia in Northern Scotland. Lancet. 1986;**1**:266

[16] Dickinson H, Parker L. Quantifying the effect of population mixing on childhood leukaemia risk: The Seascale cluster. British Journal of Cancer. 1999;**81**(1):144-151

[17] O'Donnell RG, Mitchell PJ, Priest ND, Strange L, Fox A, Henshaw DL, et al. Variations in the concentration of plutonium, strontium-90 and total alpha-emitters in human teeth collected within the British Isles. Science of the Total Environment. 1997;**201**(3):235-243

[18] Popplewell DS, Ham GJ, Johnson TE, Barry SF. Plutonium in

autopsy tissues in Great Britain. Health Physics. 1985;**49**(2):304-309

[19] Busby C. Radiation from Sellafield and Cancer near the Irish Sea: Second Report from the Irish Sea Group in Support of the Litigation Short and Others vs. BNFL and the Attorney General. Aberystwyth: Green Audit; 2000

[20] Busby C. Nuclear Pollution, Childhood Leukaemia, Retinoblastoma and Brain Tumours in Gwynedd and Anglesey Wards near the Menai Straits, North Wales 2000-2003. Green Audit; 2004

[21] Crouch D. Science and trans-science in radiation risk assessment: Child cancer around the nuclear fuel reprocessing plant at Sellafield, U.K. Science of the Total Environment. 1986;**53**(3):201-216. DOI: 10.1016/0048-9697(86)90133-6

[22] Popplewell DS, Ham GJ, McCarthy W, Morgan M. Isotopic composition of plutonium in human tissue samples determined by mass spectrometry. Radiation Protection Dosimetry. 1989;**26**(1-4):313-316. DOI: 10.1093/oxfordjournals.rpd.a080423

[23] Omar RZ, Barber JA, Smith PG. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British nuclear fuels. British Journal of Cancer. 1999;**79**:1288-1301

[24] Gillies M, Kuznetsova I, Sokolnikov M, Haylock R, O'Hagan J, Tsareva Y, et al. Lung cancer risk from plutonium: A pooled analysis of the Mayak and Sellafield Worker Cohorts. Radiation Research. 2017;**188**(6):725-740. DOI: 10.1667/RR14719.1

[25] Clarke RH, Dunster J, Nenot J-C, Smith H, Voeltz G. The environmental safety and health implications of plutonium. Journal of Radiological Protection. 1996;**16**(2):91

[26] Lisco H. Autoradiographic and histopathologic studies in radiation carcinogenesis of the lung. Laboratory Investigation. 1959;**8**(1)

[27] Taylor GN, Gardner P, Mays CW, Wrenn ME, Charrier K. Incidence of plutonium-induced bone cancer in neutered mice. Cancer Research. 1981;**41**(3):971-973

[28] Jones CW, Mays CW, Taylor GN, Lloyd RD, Parker SM. Reducing the risk of Pu-239 by chelation therapy. Radiation Research. 1986;**107**(3):296-306. DOI: 10.2307/3576834

[29] Fukuda S, Iida H, Hseih YY, Chen W. Effects of CBMIDA [Catechol-3, 6-bis (methyleiminodiacetic acid)] on removal of plutonium in rats. Japanese Journal of Health. 1992;**27**(1):11-15. DOI: 10.5453/jhps.27.11

[30] Yamada Y, Oghiso Y. Mutations in Tp53 gene sequences from lung tumors in rats that inhaled plutonium dioxide. Radiation Research. 1999;**152**(6s):S107-S109. DOI: 10.2307/3580125

[31] Kelly G, Stegelmeier BL, Hahn FF. p53 alterations in plutonium-induced F344 rat lung tumors. Radiation Research. 1995;**142**(3):263-269. DOI: 10.2307/3579134

[32] Belinsky SA, Kling DM, Liechty KC, March TH, Kang T, Gilliland FD, et al. Plutonium targets the p16 gene for inactivation by promoter hypermethylation in human lung adenocarcinoma. Carcinogenesis. 2004;**25**(6):1063-1067. DOI: 10.1093/carcin/bgh096

[33] Bair WJ, Thompson RC. Plutonium: Biomedical research. Science. 1974;**183**:715-722

[34] Gillett NA, Stegelmeier BL, Kelly G, Haley PJ, Hahn FF. Expression

of epidermal growth factor receptor in plutonium-239-induced lung neoplasms in dogs. Veterinary Pathology. 1992;**29**:46-52. DOI: 10.1177/030098589202900106

[35] Nielsen CE, Wang X, Robinson RJ, Brooks AL, Lovaglio J, Patton KM, et al. Carcinogenic and inflammatory effects of plutonium-nitrate retention in an exposed nuclear worker and beagle dogs. International Journal of Radiation Biology. 2014;**90**(1):60-70. DOI: 10.3109/09553002.2014.859765

[36] Tawn EJ, Hall JW, Schofeld GB. Chromosome studies in plutonium workers. International Journal of Radiation biology and Related Studies in Physics, Chemistry and Medicine. 1985;**47**(5):599-610. DOI: 10.1080/09553008514550831

[37] Whitehouse CA, Tawn EJ, Riddell AE. Chromosome aberrations in radiation workers with internal deposits of plutonium. Radiation Research. 1998;**150**(4):459-468. DOI: 10.2307/3579666

[38] Griffiths SD, Marsden SJ, Wright EG, Greaves MF, Godhead DT. Lethality and mutagenesis of B lymphocyte progenitor cells following exposure to α-particles and X-rays. International Journal of Radiation Biology. 1994;**66**(2):197-205. DOI: 10.1080/09553009414551101

[39] Kadhim MA, Lorimore SA, Townsend KMS, Goodhead DT, Buvkle VJ, Wright EG. Radiation-induced genomic instability: Delayed cytogenetic aberrations and apoptosis in primary human bone marrow cells. International Journal of Radiation Biology. 1995;**67**(3):287-293. DOI: 10.1080/09553009514550341

[40] Vral A, Cornelissen M, Thierens H, Louagie H, Philippe J, Struckmans K, et al. Apoptosis induced by fast neutrons versus 60Co gamma-rays in human peripheral blood lymphocytes. International Journal of Radiation Biology. 2009;**73**(3):289-295. DOI: 10.1080/095530098142383

[41] Abdelrazzak AB, Stevens DL, Bauer G, O'Neill P, Hill MA. The role of radiation quality in the stimulation of intercellular induction of apoptosis in transformed cells at very low doses. Radiation Research. 2011;**176**(3):346-355. DOI: 10.1667/RR2509.1

[42] Ponnaiya B, Jenkins-Baker G, Bigelow A, Marino S, Geard CR. Detection of chromosomal instability in α-irradiated and bystander human fibroblasts. Mutation Research/ Fundamental and Molecular Mechanisms of Mutagenesis. 2004;**568**(1):41-48. DOI: 10.1016/j.mrfmmm.2004.06.045

[43] Sun J-F, Sui J-L, Zhou P-K, Geng Y, Hu Y-C, Cao Z-S. Decreased efficiency of γ-ray-induced DNA double-strand break rejoining in malignant transformants of human bronchial epithelial cells generated by alpha-particle exposure. International Journal of Radiation Biology. 2002;**78**(9):773-780. DOI: 10.1080/09553000210141441

[44] Gamble SC, Myfanwy CC, Riches AC, Herceg Z, Bryant PE, Arranda JE. p53 mutations in tumors derived from irradiated human thyroid epithelial cells. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 1999;**425**(2):231-238. DOI: 10.1016/S0027-5107(99)00045-7

[45] Holm E. Plutonium in the Baltic Sea. Applied Radiation and Isotopes. 1995;**46**(11):1225-1229. DOI: 10.1016/0969-8043(95)00164-9

[46] Herrmann J, Nies H, Goroncy I. Plutonium in the deep layers of the Norwegian and Greenland Sea. Radiation Protection Dosimetry.

1998;**75**(1-4):237-245. DOI: 10.1093/oxfordjournals.rpd.a032237

[47] Stepanov AV, Tsvetkov OS, Tishkov VP, Belyaev BN, Donkin VD, Ivanova LM, et al. Isotopic composition of plutonium in the bottom deposits of the Norwegian Sea and Greenland Sea and identification of the sources of contaminationhearder. Atomic Energy. 1999;**87**(4):745-752

[48] Dahlgaard H. Transfer of European coastal pollution to the arctic: Radioactive tracers. Marine Pollution Bulletin. 1995;**31**(1-3):3-7. DOI: 10.1016/0025-326X(95)00003-6

[49] Lindahl P. studies of long-lived radionuclides in the environment—With emphasis on ^{99}tc, ^{237}np and pu isotopes [thesis dissertation]. Lund University Hospital, Department of Radiation Physics; 2003. ISBN: 91-974444-0-5

[50] Lindahl P, Roos P, Holm E, Dahlgaard H. Studies of Np and Pu in the marine environment of Swedish–Danish waters and the North Atlantic Ocean. Journal of Environmental Radioactivity. 2005;**82**(3):285-301. DOI: 10.1016/j.jenvrad.2005.01.011

[51] Gafvert T, Heldal H, Brungot L, Gwynn J, Stralberg E, Svaeren I, Stromsnes H, Kolstad A, Moller B, Komperod M, Lind B, Rudjord A. Radioactivity in the Marine Environment 2010. Results from the Norwegian Marine Monitoring Programme (RAME). StrålevernRapport. 2012

[52] Skwarzec B. Polonium, uranium and plutonium in the southern Baltic ecosystem. Czechoslovak Journal of Physics. 1999;**49**(1):461-466

[53] Strumińska DI, Skwarzec B. Plutonium concentrations in waters from the southern Baltic Sea and their distribution in cod (*Gadus morhua*) skin and gills. Journal of Environmental Radioactivity. 2004;**72**(3):355-361. DOI: 10.1016/S0265-931X(03)00220-0

[54] Yao Y, Volchek K, Lambert P, Brown CE. Environmental Impacts of the Fukushima and Chernobyl Accidents and their Remediation: A Review. Ottawa, Canada: Emergencies Science and Technology, Environment Canada, Atomic Energy of Canada Limited, International Safety Research Inc.; 2014

[55] Denmeade SR, Isaacs JT. Programmed cell death (apoptosis) and cancer chemotherapy. Cancer Control. 1996;**3**(4):303-309

[56] Martin KR. Targeting apoptosis with dietary bioactive agents. Experimental Biology and Medicine. 2006;**231**:117-129

[57] Lijinsky W. Chemistry and Biology of N-Nitroso Compounds. The Edinburgh Building, Cambridge, UK: Cambridge University Press; 1992

[58] Mondello C, Chiodi I. Cellular immortalization and neoplastic transformation simultaneous, sequential or independent? Telomeres, telomerase or karyotypic variations? Cell Cycle. 2013;**12**(11):1804-1805

[59] Siddoo-Atwal C. Heavy metal carcinogenesis: A possible mechanistic role for apoptosis. Vegetos. 2017;**30**(Special):125-132. DOI: 10.5958/2229-4473.2017.00046.5

[60] USNRC—Backgrounder on plutonium. 2017. Available from: www.nrc.gov

[61] Tanaka IB, Tanaka S, Ichinohe K, Matsushita S, Matsumoto T, Otsu H, et al. Cause of death and neoplasia in mice continuously exposed to very low dose rates of gamma rays. Radiation Research. 2007;**167**(4):417-437

[62] Meijer AE, Ekedahl J, Castro JB, et al. High-LET radiation induces

apoptosis in lymphoblastoid cell lines derived from ataxia-telangiectasia patients. International Journal of Radiation Biology. 2001;**77**(3):309-317

[63] Urashima T, Nagasawa H, Kassis A, et al. Induction of apoptosis in human tumour cells after exposure to augur electrons: Comparison with gamma-ray exposure. Nuclear Medicine and Biology. 2006;**33**(8):1055-1063

[64] Barillet S, Adam C, Palluel O, Devaux A. Bioaccumulation, oxidative stress, and neurotoxicity in *Danio rerio* exposed to different isotopic compositions of uranium. Environmental Toxicology & Chemistry. 2007;**26**(3):497-505

[65] Rouas C, Bensoussan H, Suhard D, Tessier C, Grandcolas L, Rebiere F, et al. Distribution of soluble uranium in the nuclear cell compartment at subtoxic concentrations. Chemical Research in Toxicology. 2010;**23**(12):1883-1889

[66] Yazzie M, Gamble SL, Civitello ER, Stearns DM. Uranyl acetate causes DNA single strand breaks in vitro in the presence of ascorbate (vitamin C). Chemical Research in Toxicology. 2003;**16**(4):524-530

[67] Miller AC, Stewart M, Brooks K, Shi L. Page N depleted uranium-catalyzed oxidative DNA damage: Absence of significant alpha particle decay. Journal of Inorganic Biochemistry. 2002;**91**(1):246-252

[68] Chapter 5: Potential human health effects of uranium mining, processing, and reclamation. In: Uranium Mining in Virginia: Scientific, Technical, Environmental, Human Health and Safety, and Regulatory Aspects of Uranium Mining and Processing in Virginia. National Academies Press; 2012

[69] Hon Z, Osterreicher J, Navratil L. Depleted uranium and its effects on humans. Sustainability. 2015;**7**(4):4063-4077

[70] Ng CY, Pereir S, Cheng SH, Adam-Guillermin C, Garnier-Laplace J, Yu KN. Combined effects of depleted uranium and ionizing radiation on zebrafish embryos. Radiation Protection Dosimetry. 2015;**167**(1-3):311-315

[71] Siddoo-Atwal C. AT, apoptosis, and cancer: A viewpoint. Indian Journal of Ecology. 2009;**36**(2):103-110

[72] Siddoo-Atwal C. Chapter 7—An approach to cancer risk assessment and carcinogenic potential for three classes of agricultural pesticides. In: Peshin R, Dhawan AK, editors. Natural Resource Management: Ecological Perspectives. Springer; 2019

[73] Human Health Fact Sheet—Plutonium. 2001. Available from: www.globalsecurity.org

[74] Langham WH, Bassett SH, Harris PS, Carter RE. Distribution and excretion of plutonium administered intravenously to man. Health Physics. 1980;**38**:1031-1060

[75] Nakashima M, Kondo H, Miura S, Soda M, Hayashi T, Matsuo T, et al. Incidence of multiple primary cancers in Nagasaki atomic bomb survivors: Association with radiation exposure. Cancer Science. 2007;**99**:87-92

[76] Shichijo K, Takatsuji T, Fukumoto M, Nakashima M, Matsuyama MM, Sekine I. Autoradiographic analysis of internal plutonium radiation exposure in Nagasaki atomic bomb victims. Heliyon. 2018;**4**(6). DOI: 10.1016/j.heliyon.2018.e00666

[77] Lambert B, Holmberg K, Hackman P, Wennborg A. Radiation induced chromosomal instability in human T-lymphocytes. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis.

1998;**405**(2):161-170. DOI: 10.1016/S0027-5107(98)00133-X

[78] Siddoo-Atwal C. A case-study of uranium and heavy metal detoxification. Indian Journal of Ecology. 2019;**46**(2):427-430

[79] Siddoo-Atwal C. Chapter 17—Biological effects of uranium and its decay products on soil microbes, plants, and humans. In: Varma A et al., editors. Plant Microbe Interface. Springer; 2019. (In press)