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Radon: Dr. Jekyll or Mr. Hyde?

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Abbreviations

αANP:	alpha-atrial natriuretic polypeptide
EPA:	environmental protection agency
Rn:	radon
ROS:	reactive oxygen species

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Abstract:

Radon (Rn) is both therapeutic and harmful to the human body. Rn is used in hot spring therapy to treat asthma, rheumatoid arthritis and hypertension patients. However, Rn is also believed to be a significant cause of lung cancer in the US. Long term exposure to Rn is believed to cause significant DNA damage. Rn is a colorless, odorless and tasteless radioactive gas. Rn is a daughter nuclide of the uranium-238 decay chain. It has a half-life of approximately 3.8 days and it decays emitting α particles, which are high level energy transfer particles. The mechanism by which Rn induces both health and harm in the body is believed to be through the formation of free radicals and more specifically reactive oxygen species (ROS). More detailed studies are required to understand the full mechanism of the benefits and the damage caused by Rn and its progeny in the body. However, since Rn exposure studies seem to point in both directions, Rn therapy should be limited only to the absolutely necessary cases.

Introduction:

Radon (Rn) comes from radium. It was originally named niton, from Latin nitens, which means shining[†]. Radon was first discovered by Fredrich Ernst Dorn in Germany in1898[‡] and in 1908, Ramsay and Grey were the first scientists to isolate it and determine its density. They were also the ones to name it niton[†]. Rn has the highest density among gases, making it the heaviest gas presently known. In 1923, it was officially named radon[†]. Rn mainly comes from the decay of radium in the earth's crust[‡]. It is mainly found in soil and sea water. In soil the highest concentration can be up to 1 g per square mile and a depth of six inches. Its concentration in sea water has been found to be between 9 and 15 ppm[‡].

Chemistry:

Understanding Rn chemistry is very important given its dual nature as both therapeutic and hazardous chemical. Rn is the 86th element in the periodic table. It is a member of group VIIIA and a noble gas because of its inert nature. It is colorless, odorless and tasteless, which makes it even more dangerous as a gas, since it is radioactive. Its atomic mass is 222.02 amu and its atomic radius is 1.34 Å. Its boiling point is -62^{o}C (-80 F) and its density is 9.73 g/L at standard temperature and pressure[†].

Rn, being a radioactive gas, emits radiation. There are three main types of radiation: α radiation, β radiation and γ radiation. In α radiation, α particles or Helium nuclei ($_{2}^{4}He$) are spontaneously emitted from the nucleus of the atom [1]. In β radiation, β particles or high-speed electrons ($_{-1}^{0}e$ or $_{-1}^{0}\beta$) are emitted from the nucleus. In γ radiation (or γ rays), high energy photons ($_{0}^{0}\gamma$) are emitted. The γ rays are the most damaging particles, because their penetrating

[†] Taken from Los Alamos Nat'l Laboratories: http://pearl1.lanl.gov/periodic/elements/86.html accessed on 2/10/05

[‡] Taken from: http://environmentalchemistry.com/yogi/periodic/Rn.html accessed on 2/10/05

power is about 10,000 times that of the α particles [1]. Rn is an α particle emitter and it is part of the uranium-238 ($^{238}_{92}U$) decay chain. The main reactions for this decay chain are pictured below [1, 2]:

$^{238}_{92}U \Rightarrow {}^{234}_{90}Th + {}^{4}_{2}He$	α emission	**Reaction 1**
$^{234}_{90}Th \Rightarrow {}^{234}_{91}Pa + {}^{0}_{-1}\beta$	β emission	**Reaction 2**
$^{234}_{91}Pa \Rightarrow {}^{234}_{92}U + {}^{0}_{-1}\beta$	β emission	**Reaction 3**
$^{234}_{92}U \Rightarrow {}^{230}_{90}Th + {}^{4}_{2}He$	α emission	**Reaction 4**
$^{230}_{90}Th \Rightarrow {}^{226}_{88}Ra + {}^{4}_{2}He$	α emission	**Reaction 5**
$^{226}_{88}Ra \Rightarrow {}^{222}_{86}Rn + {}^{4}_{2}He$	α emission	**Reaction 6**
$^{222}_{86}Rn \Rightarrow {}^{218}_{84}Po + {}^{4}_{2}He$	α emission	**Reaction 7**
$^{218}_{84}Po \Rightarrow {}^{214}_{82}Pb + {}^{4}_{2}He$	α emission	**Reaction 8**
$^{214}_{82}Pb \Rightarrow {}^{214}_{83}Bi + {}^{0}_{-1}\beta$	β emission	**Reaction 9**
$^{214}_{83}Bi \Rightarrow {}^{210}_{81}Tl + {}^{4}_{2}He$	α emission	**Reaction 10**
$^{210}_{81}Tl \Rightarrow {}^{210}_{82}Pb + {}^{0}_{-1}\beta$	β emission	**Reaction 11**
$^{210}_{82}Pb \Rightarrow {}^{210}_{83}Bi + {}^{0}_{-1}\beta$	β emission	**Reaction 12**
$^{210}_{83}Bi \Rightarrow {}^{206}_{81}Tl + {}^{4}_{2}He$	α emission	**Reaction 13**
$^{206}_{81}Tl \Rightarrow {}^{206}_{82}Pb + {}^{0}_{-1}\beta$	β emission	**Reaction 14**

Radon has three isotopes: radon, toron and actinon and all three are α emitters [3]. Radon has a half life of about 3.8 days and it decays to unstable isotopes of polonium, lead, tellurium and bismuth according to the reactions above. Since Rn is a product of the uranium-238 decay chain, its concentration depends on the concentration of uranium in rocks and water deposits. Uranium is found in small concentrations in all types of rocks, but the highest concentrations are found in volcanic rocks, granites and sedimentary rocks [3]. Uranium concentrations in these types of rocks can reach approximately 100 ppm [3]. Water that comes from rocks that are rich in uranium will frequently have concentrations of dissolved Rn (produced from the uranium decay) that range between 500 Bq L^{-1} as a lower limit, up to 20,000─60,000 Bq L^{-1}(Bq is the SI unit for radioactivity called Becquerel and it is equal to one disintegration per second). The other radioactive unit that is still being used is named after the French physicist Marie Curie and it is given as picoCuries-pCi (1 pCi = 0.037 Bq) [3]. According to the EPA (Environmental Protection Agency) the upper Midwest and the Northeast have the highest radon gas concentrations in US. Iowa and North Dakota have the highest levels of Rn gas in air with over 4 pCi/L of Rn in indoor air in all their counties[††] (4 pCi/L is the EPA standard concentration for Rn gas in indoor air).

As mentioned above, Rn is extremely soluble in water (500 mL of Rn gas dissolve in 1 L of water at 0^oC). It is 7.6 times heavier than air, which is why it accumulates in the basements or underground levels of buildings [3]. EPA has set the Rn concentration standard for drinking water at 300 pCi/L[‡‡] (the fact that air concentration standards for Rn are so much lower than the standard concentrations for water suggests that Rn is much more hazardous if inhaled through air, rather than ingested through drinking water). Most of Rn gas that is inhaled through indoor air comes from Rn evaporation from Rn rich waters. Once Rn gets inhaled into the lungs it will diffuse in the bloodstream and will decay into its daughter isotopes and release α particles. Rn is lipid soluble so it will accumulate in organs rich in fat such as endosecretory glands and nerve fibers [4]. α-Particles penetrate only approximately 20 μm (approximately two cell diameters) through body tissues [4]. This process implicates that continuous exposure to Rn and its progeny (whether inhaled as a gas or ingested as water) will lead to lung, stomach and colon cancer [3]. Rn is also suspected to be the cause of some cases of leukemia [3].

On the other hand, low irradiation doses of Rn gas have been used in hot spring therapy to treat asthma and diabetes patients [3, 4, 5]. Rn, whether inhaled as a gas, ingested as water

[††]From EPA website http://www.epa.gov/radon/zonemap.html accessed on 2/20/05

[‡‡] From EPA http://www.epa.gov/safewater/radon/proposal.html accessed on 2/20/05

enriched Rn or used in water and mud baths has also been utilized to treat rheumatism, the nervous system and the cardiovascular system all over the world [3].

Radon therapy

It is thought that one of the main causes of asthma symptoms (edema, mucous secretion and bronchoconstriction) is the production of ROS (reactive oxygen species) such as H_2O_2, $O_2^{\bullet -}$ and $HO^{\bullet}$, by inflammatory cells [4]. The main enzymatic defense against these ROS in the lungs include: catalase (CAT) and superoxide dismutase (SOD). A study was conducted to correlate Rn therapy with asthma [4]. Rn therapy with a concentration of 2,080 Bq L^{-1}(and a temperature of 48°C and high humidity) was carried out for 40 min, once a day. It was found that the activity of CAT was considerably increased and the lipid peroxide level was considerably decreased as compared to the control [4]. Even though most of Rn disappears shortly after it enters the body, it releases a large amount of energy that gets absorbed by tissues. This transfer of energy initiates a cascade of radicals that stimulates detoxification processes and may facilitate the induction of protective enzymes and alter cell metabolism [4].

Similar studies as with the asthma patients were conducted with arthritis, diabetes and hypertension patients [5]. Rn concentration was 2,080 Bq L^{-1} with a 36°C temperature. Subjects were exposed to Rn gas for 40 min once a day. These studies showed an increase in the level of αANP, which causes the vascular smooth muscles to relax and the blood pressure to decrease [5]. Pain alleviation was also observed, because the levels of β endorphin and ACTH (from the adrenal cortex) were considerably increased [5, 6]. No significant changes were observed in blood glucose and glucagons levels [5]. These studies also observed that there was a 4% increase in percentage of the level of CD4 positive cells (the markers of helper T cells) and a 5% decrease in percentage of the level of CD8 positive cells (the marker of killer T-cells) suggesting that Rn therapy enhances the immune system [5]. The nucleus ability to repair its DNA has been observed to increase with low level radiation, which implies that DNA that is damaged in a disease can be restored faster and perhaps, more effectively [6]. These results were obtained by using high-dose Rn radiation for short periods of time.

Radon and cancer

It is believed that 10% of all lung cancer deaths and as high as 30% of lung cancer deaths among non-smokers in the US are caused by Rn exposure. More than 16,000 lung cancer cases a year are attributed to Rn [7]. This makes Rn exposure the second leading cause of lung cancer next to smoking. The lung epithelial cells are thought to be damaged either through the nucleus DNA being damaged directly by the radiation, or from the free radical formation [7]. The radiation of α particles gets transferred to a very concentrated region in the body (mainly in the epithelial cells in the lungs). It has been measured that approximately 80% of the radiation will get absorbed by water molecules and will eject a free electron (see **Reaction 15**):

$H_2O \rightarrow H_2O^+ + e^-$ **Reaction 15** [7]

The ejection of a free electron leads to the formation of such reactive species such as: e^-_{aq}, $HO^\bullet$, $H^\bullet$ and H_2O_2. The hydroxyl radical $HO^\bullet$ is the most oxidizing radical formed *in vivo*. The hydroxyl radical will initiate a cascade of oxidative damage, such as lipid peroxidation and DNA damage (**Reactions 16 & 17**) to the surrounding area where it is formed [8].

$HO^\bullet + L\text{-}H \rightarrow L^\bullet + H_2O$ **Reaction 16** **[** [8]

$HO^\bullet + \text{Base} \rightarrow \text{HO-Base}^\bullet$ **Reaction 17** [8]

The ejected electrons will quickly react if oxygen is present to form superoxide $O_2^{\bullet -}$, which can undergo dismutation reactions and produce H_2O_2 (**Reactions 18 & 19**) [8].

$e^-_{aq} + O_2 \rightarrow O_2^{\bullet -}$ **Reaction 18** [8]

$2O_2^{\bullet -} + 2H^+ \rightarrow O_2 + H_2O_2$ **Reaction 19** [8]

Superoxide and hydrogen peroxide are relatively stable and have a longer half-life so they can diffuse further into cells and initiate Fenton reactions inside cells (**Reactions 20 & 21**)[8].

$Fe^{III} + O_2^{\bullet -} \rightarrow Fe^{II} + O_2$ **Reaction 20** [8]

$Fe^{II} + H_2O_2 \rightarrow HO^{\bullet} + HO^{-} + Fe^{III}$ **Reaction 21** [8]

The formation of the $HO^{\bullet}$ radical propels the system on the top of the pecking order and other oxidation reactions can occur. As a consequence cells that display higher ROS enzyme activity are less severely affected by radiation. The exact mechanism by which α radiation induces lung cancer is not known, however it is known that radiation can cause DNA damage such as gene mutations, chromosomal damage and sister chromatid exchange [7]. It is also found that directly irradiated and damaged cells can cause neighboring cells (that were not directly irradiated) to undergo damage by a phenomenon called the by-stander effect [7, 9]. This phenomenon is caused by cross talk between neighboring cells through either a physical connection (such as cells touching each other) via gap junctions, or a medium [9]. Thus, a direct radiation traversal through a nucleus is not essential for genetic damage to occur [10]. Studies have implicated connexin43 gap junctions in connection to the cell response to radiation and bystander effects [10]. Octanol, a gap junction inhibitor, was found to reduce the mutation yields [11]. Other studies show that induced DNA damage is not the only target of low dose radiation [11]. Irradiation of cellular cytoplasm has been observed to induce mutations in the nuclei of irradiated cells and this process occurs by the production of oxyradicals [11].

A possible mechanism that has been proposed is the free radicals that are produced during the irradiation of the cytoplasm amplify lipid peroxidation processes [12]. Mitochondrial damage byproducts such as peroxynitrite anions could also be involved [12]. Studies conducted with p53 (a tumor suppressor gene, which gets mutated in approximately half of human cancers) in irradiated NHBE cells, show that transitions such as G → A at codon 249 (AGG → A<u>A</u>G) and

C → A at codon 250 (CCC → <u>A</u>CC) occur [13]. It is believed that C → A conversions occur through energy deposition in neighboring C residues [13]. Other mutations that have been found in Tp53 include C→ T transitions [13, 14]. These C → T transitions are thought to occur through $NO^{\bullet}$ radicals that deaminate cytosine and methyl cytosine residues [13, 14]. Airway lining fluids are suspected of being a mediator of bystander effects between irradiated and non-irradiated cells [15]. *In vitro* studies conducted with serum containing media have shown that the irradiated serum can act as a source of induced mutations (sister chromatid exchange) [15]. In fact these mutations are of approximately the same magnitude as the mutations induced by directly irradiating the cells [15]. All the above studies were conducted to mimic long term exposure to Rn.

Conclusion

So is Rn Dr. Jekyll or Mr. Hyde? Evidence seems to point out that Rn can do both: help and harm the human body. This seems to depend on the dose and the amount of time of exposure to Rn radiation. Rn can be harmful to the human body if inhaled for long periods of time. Numerous studies have been conducted that link Rn long term exposure to DNA damage and mutations via induced free radical formation. On the other hand, high-dose exposures to Rn for short periods of time can prove to be beneficial to patients with asthma and rheumatoid arthritis. However, since Rn exposure studies seem to point in both directions, Rn therapy should be limited only to the absolutely necessary cases and care should be taken to raise awareness on the dangers of living with Rn.

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