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REVIEW PAPER

Excellence is the Real Enemy of Practicality! Relevance to Radiation Countermeasure Development

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ABSTRACT

Radiation countermeasures development was undertaken almost six decade ago at AFRRI, USA with the aim to protect military as well as civilian personals against accidental or deliberate radiation exposure. Later on, with the advancement of radiation technologies and exploration of X-ray or γ-rays for diagnostics and therapeutic purposes, probability of radiation exposure was enhanced multifold. Therefore, importance of radiation countermeasures development was recognised globally. However, despite the concentrated efforts, till date not a single FDA approved radio protective drug is available for emergency uses. Major impediments identified in this are included variability in radio protective efficacy with different experimental models, radiation dose rate, radiation types and differential radio sensitivity of various biological systems. No way to evaluate radio protective efficacy of an agent in human volunteers. It is sufficient to realise that uniform excellence may not be achieved in the area of radiation countermeasure development. However, practical excellence based on the radioprotector's application scenario can be achieved. Different radiation accidental scenarios and feasible practical parameters of excellence for radiation countermeasure development for particular types of incidental, accidental or deliberated radiation exposure are described.

Keywords: Radiation countermeasure; Gamma radiation; Nuclear accidents; Radiation damage; Medical management

1. INTRODUCTION

Radiation, is an integral part of the universe functioning. Even, life forms are evolved in a radiation rich environment[1-3]. Radiation is a wave of energy that is made-up of streams of particle called photons. There are different kinds of radiation exists all around us like 'visible light' help us to visualise, ultraviolet radiation used for sterilisation, infrared radiation (heat energy used in microwave oven), sound, phone, radio and television signals[4], etc. Basically, atom conserved energy that released in the form of radiation either upon atomic structure disintegration (fission reaction) or integration (fusion reaction). The common source of electromagnetic radiation on the earth is the nuclear fusion reaction continuing on the Sun where hydrogen atoms gets fused into helium and atomic mass difference transforming into solar radiation. Based on the energy carrying potential of the wave photons that can either excite and ionise or only excite but not ionise the atoms or molecules, radiation is categorised as ionising radiation and non ionising radiation.

Ionising radiation is described as the amount of energy capable to knockout the electrons from their set orbits around atomic nucleus resulted imposed positive charge on the atom. These electrically charged molecules and atoms are called ions. Examples of Ionising radiation includes cosmic radiation in the space, gamma rays used during radiotherapy of cancer patients, positron beam used during Positron Emission Tomography (PET) scanning, radioisotopes used for scintigraphy purposes, X rays used for human diagnostics[5], Iodine-131 isotope used for thyroid cancer detection, phosphorus-32, and Tritium-99 used for research purposes and nuclear radiation (alpha, beta particles, gamma rays and neutrons) generated from the nuclear reactor accidents (Chernobyl in USSR, Fukushima in Japan) or nuclear bomb explosion (Hiroshima and Nagasaki) in Japan[6]. Ionising radiation carries tremendous amount of energy that oxidise the molecules come in its path. In biological systems ionising radiation induces radiolysis of water and thus produces free radicals that further accelerate oxidation of other vital molecules lead to chemical and thus biological reactions impairment lead to cell death. Based on energy strength and mass of the energy particles, ionising radiation is further categorised as low LET and high LET radiation. Gamma and X-rays have maximum penetration power because they have less mass and high energy and thus belongs to low LET radiation category. On the other hand alpha, beta particles and neutron carries sufficiently high energy but heavy mass. Therefore, they cannot travel to a long distance and thus have low penetrating power are classified as high LET radiation. Gamma radiation consists of photons that originate from the nucleus[6]. While, X-ray radiation consists of photons that originate from outside the nucleus, and relatively have lower energy than gamma radiation. Photon radiation (γ and X rays

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both) can penetrate very deeply inside the objects including human tissues and organs come across their path[7].

2. NATURAL SOURCES OF IONISING RADIATION

Radiation is always present around us. A hypothesis[1-3] explained that how life was evolved on the earth in the presence of ionising radiation. Being the part of evolution, ionising radiation has significant effect on chemical and biological evolution. Many naturally occurring radioisotopes are primitively formed by interaction of cosmic rays with the molecules in the atmosphere. Tritium is an excellent example of a radioisotope that formed by cosmic ray's interaction with atmospheric molecules. Some radioisotopes such as Uranium and Thorium were formed at the time of solar system evolution. These radioisotopes have billions of year's half life and still contributing to the background radiation in the natural environment[8].

3. RADIATION

The earth's outer atmosphere is continually bombarded by cosmic radiation. Cosmic rays are ultra-high energy (range 100-1000 TeV) radiation which originating outside the solar system, wide-spreading across our Milky Way galaxy and striking the Earth continuously from the space. Victor Hess discovered cosmic rays. He has observed that an electroscope discharged more frequently as it ascended at higher atmosphere with a balloon. Victor Hess has attributed this phenomenon with the radiation that entering the atmosphere from outer space[9]. The energy of cosmic rays is usually measured in the units of Mega-electron volts (MeV) or in Giga-electron volts (GeV). The highest energy cosmic rays measured to date had more than 10^{20} eV. Intensity of cosmic radiation increases with increasing altitude, suggested their origin from outer space. Further, intensity of the cosmic rays changes with the latitude, suggested presence of charged particles in the cosmic rays composition that was affected by the earth's magnetic field. Cosmic rays general composition[10] is as: ~90 per cent protons (hydrogen nuclei), ~9 per cent alpha particles and ~1 per cent electrons. Cosmic rays may also have a small fraction of heavier particles and about ~0.25 per cent light elements like lithium, beryllium and boron). Cosmic rays density in the interstellar space is estimated to be about $10^{-3}/m^3$. It has been observed that high energy collisions in the upper atmosphere produce cascades of lighter particles like Pions and Kaons. These light particles are further decayed and produced Muons. According to an estimate, Muons is contributed to more than a half of the total cosmic radiation. Surprisingly, presence of isotope ^{10}Be (half-life of 1.6 million years) in the cosmic ray, implies that, on an average, cosmic rays spend about 10 million years in the galaxy before escaping into inter-galactic space. Although, thousands of cosmic rays passed across our body every day, however, their radiation level is extremely low[11]. However, the greater intensity of cosmic rays in outer space is a potential threat for astronauts.

4. TERRESTRIAL RADIATION

Potassium, uranium and thorium and their decaying products such as radium and radon are the major contributors of terrestrial radiation on earth. Most of the naturally occurring unstable radionuclides are converting into their stable element by the process of continuous radioactive decay. Thus, the present radioactivity on the earth from Uranium-238 remained only half as it originally was form, because of its 4.5 billion year half-life. Similarly, Potassium-40 (half-life 1.25 billion years) is remaining only about 8 per cent of its original radioactivity. The adverse effects of actual diminishment (due to decay) of these isotopes on humans life will not be significant, because, human history is so short in comparison[12-13].

5. MAN MADE SOURCE OF RADIATION

The most common sources of man-made radiation exposure to the human are medical procedures, i.e. diagnostic X-rays, CT scanner, PET scanner, nuclear medicine, and radio-therapy unites. In addition, peoples are also exposed to radiation from consumer products containing radioactivity, such as tobacco products (contain thorium), smoke detectors (contain Americium), luminous watches (contain Tritium), construction materials, eye glass, televisions screens, airport X-ray systems, electron tubes, fluorescent tube starters, lantern mantles (contain thorium), etc. Peoples can also expose to radiation during mining and milling of uranium to produce nuclear energy. Radiological dispersal devices (RDD) can be a prominent man-made source of radiation. Besides these, the most significant source of nuclear radiation exposure to the general public is the nuclear power plant accidents like Chernobyl (USSR) and Fukushima (Japan). Finally, nuclear weapon detonation during testing or attack may contribute substantially to the general public radiation exposure[14].

6. BIOLOGICAL DAMAGE SCALE OF NUCLEAR RADIATION: INVERSE SQUARE LAW AND THE RULE OF SEVEN

Biological damage induced by ionising radiation depends on its distance from the victim and energy levels (dose rate). Radiation (gamma or X-ray) emission strictly obeys the inverse square law. According to this law, the intensity of radiation becomes weaker as it spreads out from the source over a larger geometrically uniform area. Therefore, in principle, the intensity of radiation will be inversely proportional to the square of the distance from the source. It is true because the surface area of a sphere increases with the square of the radius. It means, if a person stand twice as far away from the radiation source, he will receive only one-quarter (1/4th) of the radiation energy as compared to the person stand at the point of radiation source in the equal time frame. Inverse square law can be understood in the nature by calculating the difference in intensity of solar radiation at different planets. The intensity of solar radiation release from the Sun is calculated as 9126 W/m^2 at the distance of Mercury (0.387 AU), whereas, it is only 1367 W/m^2 at the distance of Earth (1 AU). Therefore, it suggested that approximately three fold increase in the distance leading to nine fold decrease in the solar radiation intensity[15-16].

7. RADIATION EXPOSURE BY ATOMIC WEAPON EXPLOSION

The energy emitted during nuclear explosion is the result of the splitting of atomic nucleus and subsequent chain reaction of radioactive materials, i.e. Uranium-235 and Plutonium-239 nucleus. The energy that released from an atomic explosion can be quantified in terms of kilotons (Kt) of the conventional explosive trinitrotoluene (TNT). The energy composition of nuclear explosion can be divided into fireball (thermal and radiation energy), blast forces/waves (high energy shock wave), prompt/early radiation (gamma rays) wave, light energy, and delayed ionising radiation that is produced by the fallout of the radionuclides generated during nuclear fission chain reaction[17]. The prompt/early radiation pulse predominantly gamma rays and neutron generates within milliseconds of detonation can cause whole body exposure and acute radiation syndrome (ARS). Atomic fission reaction is produced a mixture of about ~80 different radionuclides. These radionuclides are varied in terms of their stability. Some nuclides are completely stable while, others unstable and thus undergo radioactive decay with half-life's range from fractions of a second (short lives isotopes) to thousands of years (long lived isotopes). About >300 different isotopes belong to approximately 36 different elements have been identified in the mixture of fission reaction products. As far as concerned with the radiation effect, thumb rule is the 'rule of sevens'. This rule is explained that every seven-fold increase in the time followed by a nuclear detonation, the radiation intensity (dose) decreases by the factor of 10. For example, after 7 h of explosion, the residual radioactivity will be declined by 90 per cent. Further, it will decline again by 90 per cent after 7x7 h (49h, approximately 2 days). The radiation level will drop again by 90 per cent after 7x2 days (2 weeks). The rule of seven is accurate to 25 per cent for the first two weeks, and it is accurate to a factor of two for the first six months. After 6 months, the rate of radiation decline becomes much more fast. The radioisotopes fallout can contaminate soil, food and water supply of the surrounding area. Radiation from contaminated area can induce structural and functional damage to the biological system. Though, outcome of the biological radiation injuries depends on radiosensitivity of the involving system/organs. Radiosensitive systems like hematopoietic and gastro-intestinal system are considered more radiosensitive as compared to skin, muscular, and nervous system. Following are dose dependent biological effects of whole body gamma irradiation on human organ systems[18-20].

8. RELEVANCE AND IMPORTANCE OF RADIOPROTECTOR DEVELOPMENT

A study published by Coeytaux[21] to estimate radiation accidents worldwide within the period of 1980 to 2013, revealed that total 634 radiation accidents were reported during the years of 1980-2009, that involves 2390 overexposed peoples, out of whom 190 people died due to radiation lethal dose over exposure. This study further stated that though number of radiation accidents is decreased for all types of radiation use, but increases in the medical sector (64 per cent) particularly radiotherapy and fluoroscopy procedures.

Radiation countermeasures are extremely useful for military personnel and first responders in case of nuclear emergency. Medical management of nuclear accident is the most significant area where radiation countermeasure unavoidably applicable. The industrial sector contributes about 24 per cent of total worldwide reported radiation accidents[21]. India is expanding its nuclear energy needs and thus Indian federal government committed to increase nuclear installations. Former Indian President Late (Dr) A.P.J. Abdul Kalam, has stated while he was in the office, that *'The energy independence is India's first and highest priority milestone need to achieve as soon as possible" and therefore India has to go for nuclear power generation in a big way using thorium-based reactors'.* Indian government has ambitious plan to increase the contribution of nuclear power to expedite its electricity generation capacity from 2.8 per cent to 9 per cent within next 25 years. In view of that, the Indian nuclear power industry is expected to undergo an unprecedented expansion in the coming years. To achieve ambitious milestones of nuclear power generation, Indian government passed U.S.-India Civil Nuclear Agreement to carry out trade of nuclear fuel and technologies with other countries to enhance its power generation capacity. When this agreement implemented, India is expected to generate an additional 25,000 MW of nuclear power by the year of 2020, bringing total estimated nuclear power generation to 45,000 MW. In view of government planning to enhance nuclear power generation capacity, nuclear power reactor installations are bound to increase in future. Though, extreme safety measures are implemented for nuclear power plant safety, however still nuclear reactor incidents or accidents (level 1-7 level) cannot be ruled out completely. Available substantial evidences of level 7 nuclear reactor accidents in the past like Chernobyl in Ukraine (formerly USSR) and Fukushima in Japan are enough to understand the significance of radiation countermeasures for civilian as well as for defence sector.

Among the radiation accidents occurred worldwide since 1980-2013, most of them belong to medical procedures, either during radiation therapy (32 per cent) or fluoroscopy (31 per cent). According to the number of overexposed persons, reported accidents involving radiation therapy were greater (47 per cent), followed by accidents in the industrial sector (22 per cent), then in fluoroscopy (17 per cent) and orphan sources (9 per cent). Interestingly, the published report[21] demonstrated that though, radiation accidents and the number of exposed persons are declined significantly in all sectors dealing with radiation in the last three decades (1980-2009) except in medical sector (i.e. radiatiotherpay and medical fluoroscopy). Geographical distribution is demonstrated that medical sector accounted for maximum radiation overexposures in North America (663 cases, 91 per cent), Europe (642 cases, 93 per cent), and South America (163 cases, 61 per cent) [21]. Due to increasing cancer accidents, uses of radiation therapy are expected to increase in the future. Therefore, it is crucial to ensure high quality assurance error proved standard procedure to avoid over exposure accidents in radiotherapy patients.

8.1 Estimated Radiation dose *vs* Radiation Accidents

8.1.1 Chernobyl Radiation Accident

The Chernobyl nuclear reactor accident occurred in the very early morning of 26th April 1986 in USSR. It was the most serious accident in the history of the nuclear industry. It occurred due to meltdown of reactor core and subsequent explosion and fire. Cloud of various types of radioactive materials, especially iodine-131 and caesium-137 was spread over the Europe including Belarus and the Russian Federation. Radiation Workers who were operating near the reactor at the time of the accident exposed with high doses of gamma radiation (i.e. 2 - 20 Gy). Evacuated population from the accident area was exposed to an average radiation dose of ~33 mSv. However, some individuals were exposed to several hundred mSv of radiation doses. Through consuming contaminated food containing radioactive iodine-131, some people received very high internal doses of radiation (up to 50 Gy), particularly in the thyroid gland. Out of 134 emergency radiation workers who received high doses of radiation were diagnosed with acute radiation syndrome (ARS) and 28 of them died within a month after the accident. Chernobyl radiation accidents accounted 56 direct deaths (47 radiation workers + 9 children with thyroid cancer). However, the general population exposed to the Chernobyl fallout not suffers from ARS, as the radiation doses received by them were relatively low[22-24].

8.1.2 Fukushima Radiation Accident

Followed by a major earthquake in Japan on 11 March 2011, huge tsunami waves disrupted the power supply and cooling system of three Fukushima Daiichi reactors, causing devastating nuclear accident. The accident was rated of 7th level on the INES scale, due to high radioactivity releases (940 PBq of Iodine-131 eq). Though, there were no deaths reported due to radiation sickness, but over 100,000 people evacuated from their homes to ensure their safety. TEPCO had estimated the radiation exposure of 19,594 people who worked on the accident site. According to the reports, 167 workers exposed with radiation. Out of these 135 workers had received 100 to 150 mSv, 23 workers received 150-200 mSv. While, three workers received 200-250 mSv, and last six workers received over 250 mSv (309 to 678 mSv) apparently due to inhaling Iodine-131 fume. The highest dose rate at the site of accidents was estimated to be 300 mSv/h. Though, higher than normal doses were accumulated in hundreds of workers deployed on the accident site, but no radiation casualties (acute radiation syndrome) reported [25-28].

8.1.3 Tokaimura Radiation Accident

Tokai-mura accident (1999) occurred in a very small fuel preparation plant operated by Japan Nuclear Fuel Conversion Co. On 30th September morning, three workers initiated a preparation for a small batch of fuel for experimental purpose using enriched (18.8% U-235) uranium. Eventually, volume of reaction reached at about 40 litres containing about 16 kg Uranium. As critical mass achieved, nuclear fission chain reaction was initiated with intense gamma and neutron radiation emission. Doses assessment analysis revealed that three worker involved in that experiment received whole body radiation doses of 16-20,000 millisieverts (person-1), 6-10,000 millisieverts (Person 2) and 1-5000 millisieverts (person 3)), mainly from neutrons and died within 12 week. Absorbed dose for other 436 people was evaluated, none of them exceeded 50 mSv (the maximum allowable annual dose)[29-31].

8.1.4 Soviet Submarine K-431Radiation Accident

Soviet submarine K-431, a Soviet nuclear-powered submarine was commissioned on September 30th, 1965. An explosion occurred in this submarine during refueling at Chazhma Bay, Vladivostok. Total 10 causalities (8 officers+2 assistant) were reported in the accidents due to explosion rather radiation exposure. However, other 49 people received radiation injuries with 10 people developed radiation sickness (mostly fire-fighter). Some people exposed with 2.2 Gy external dose and 4 Gy internal dose to thyroid gland. Besides that, out of 2000 persons involved in cleanup operations, 290 received high level of radiation dose compared to normal set limit[32]. TIME magazine reported this accident as one of the world’s ‘worst nuclear disasters’.

8.1.5 Soviet Submarine K-27 Radiation Accident

On May 24th 1968, the power output of one reactor of submarine K-27 suddenly dropped and radioactive gases were released and accumulated into its engine cabin. The radiation (compositions: mainly gamma rays and thermal neutrons with alpha and beta particles) level were increased dangerously by 1.5 Gy/h. Total 9 causalities were reported due to k-27 radiation accidents[33].

8.1.6 Soviet Submarine K-19 Radiation Accident

On July 4th 1961, soviet submarine *K-19* was conducting naval exercises in the North Atlantic close to Southern Greenland under the command of Captain Nikolai Vladimirovich Zateyev. Suddenly, a substantial leakage in its nuclear reactor’s coolant system was observed. The submarine reactor temperature increased upto 800 °C due to heat generated by fission reaction. The submarine reactor continued to heat up as the required coolant was not available. Captain Zateyev ordered the team of engineers on board to fabricate a new coolant system *via* removing off an air vent valve and jointing a water-supplying pipe into it. This procedure need to work the engineers in high radiation environment for extended periods. As air vent valve removed the radioactive steam containing fission products spread into ventilation system and other compartments of the submarine. However, this procedure successfully reduced the core reactor temperature but all seven members of the engineering crew and one divisional officer on board exposed with lethal doses (11-54 Gy) of radiation and all died within a month. Besides that, 15 other sailors exposed with relatively low doses of radiation and all died within next two years[34-35].

8.2 The Goiânia Radiation Contamination Accident due to Stolen Radiation Source

On September 13th 1987, at Goiânia, in the Brazilian state of Goiás, an old radiotherapy source was stolen from the city hospital and subsequently handled by many people in the scrapyard resulted four causality as:

- Leide das Neves Ferreira, six year old daughter of Devair Ferreira the scrapyard owner was the first death out of four people exposed with stolen radioactive source. She received 6.5 Gy whole body radiation.
- Gabriela Maria Ferreira, 37 year old wife of Devair Ferreira, became sick about three days after coming in contact with the radioactive source. She received 5.7 Gy dose of radiation and died.
- Israel Baptista dos Santos, 22 year old employee of Mr. Ferreira who worked on the radioactive source primarily to extract the lead was exposed with 4.5 Gy of radiation and died.
- Admilson Alves de Souza; 18 years old another employ of Mr. Ferreira exposed with 5.3 Gy dose of radiation and died. However, surprisingly, Devair Ferreira himself was survived despite receiving 7 Gy of radiation. He died later on in 1994 due to cirrhosis aggravated by depression and binge drinking[36-37].

8.3 Cecil Kelley Criticality Radiation Accident at Los Alamos

Cecil Kelley was a chemical plant operator and operating a large (1,000 liter capacity) stainless steel plutonium mixing tank. The tank contained residual plutonium-239 remained unutilised from other experiments. Suddenly plutonium in the tank achieved criticality and incursion with flash bright light was emitted. The Kelley stand near by the tank was completely showered with the excursion mixture and heavily exposed with fast neutron (9 Gy) and gamma ray (27 Gy), total 36 Gy. Though Kelley received immediate medical support but he lost his life within 35 h after the radiation incident occurred[38-39].

8.4 Nuclear Weapon Detonation *vs* Radiation doses: A Real Experience

The only factual experience in the history of nuclear attacks is preserved with the Hiroshima and Nagashaki, Japan nuclear attack by US army in 1945. Hiroshima was blown up by Uranium bomb (based on fission principle) named "little boy" (reported yield; 16 KT), while Nagashaki was bombarded by plutonium bomb (based on fusion principle) named 'fat man' (reported yield: 21 KT). Hiroshima bomb was exploded at 600 m height from the ground. The bomb energy distribution was estimated to be as: 50% of total bomb energy was converted in to blast wave, 35% energy converted in to heat wave and 15% energy converted into radiation (10% residual + 5% instant radiation). A relationship between initial radiation reached to the hypocenter (ground zero) in Hiroshima versus distance from the ground zero was placed below (Figs. 1 and 2). Ionising radiation in the form of neutrons and gamma rays generated from the nuclear fission chain reactions was reached at ground zero even prior to the explosion occurred and affect the human body[40]. People received lethal dose of pre neutron and gamma radiation at this point died, regardless of the high pressure shock and heat waves. Various people who were involved in vigorous rescue operation at around 1,000 m to 1,500 m away from ground zero not experienced radiation sickness immediately but they suffered due to an estimated exposure radiation of 1,500 mSv to 2,500 mSv dose (Figs. 1 and 2).

8.5 Residual Radiation in Hiroshima after Nuclear Blast

Residual radiation classified in to two categories, i). Induced radiation (activated neutron reached to ground, and ii). Radiation from radioactive fallout of more than 300 radioisotopes. Induced radiation produced by the collision of ground reaching neutrons with other materials that create radionuclide. The amount of nuclides generated depends on the amount of neutrons that reach the ground. The radiation dose versus distance relationship of Hiroshima induced radiation is given in (Figs. 1 and 2). Persons remained for 100 h within 1 km of ground zero following the blast may expose one to several sieverts of radiation. Induced radiation decays to 1/100 after 30 min, 1/1000 after one day, and 1/1,000,000 after a week.

Residual radiation composed of radioactive products produced from the fission reactions blowned- up into the mushroom cloud. Due to their high mass radioactive nuclides come down in the form of black rain. The black rain contained several thousands of isotopes including of uranium 235 and plutonium 239 (half-life of 25,000 years) that did not undergo

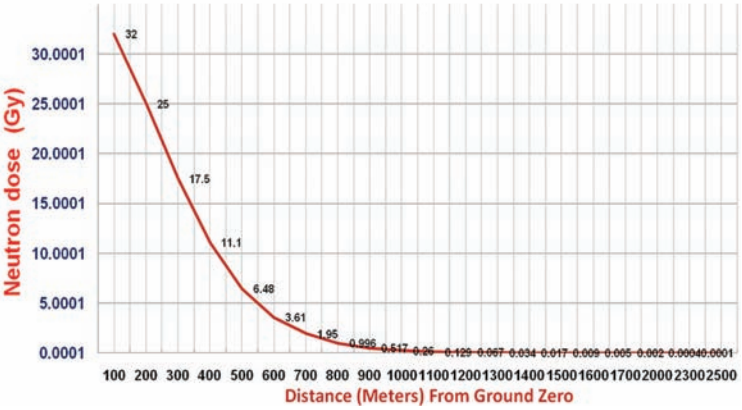


Figure 1. **Neutron radiation dose along with distance from the hypocenter of Hiroshima nuclear attack.**

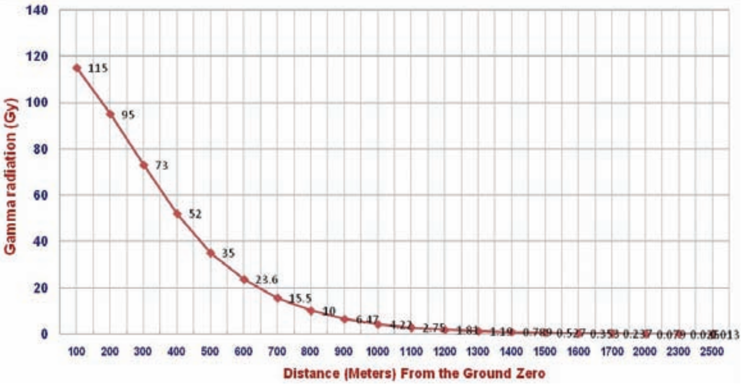


Figure 2. **Gamma radiation dose along with distance from the hypocenter of Hiroshima nuclear attack.**

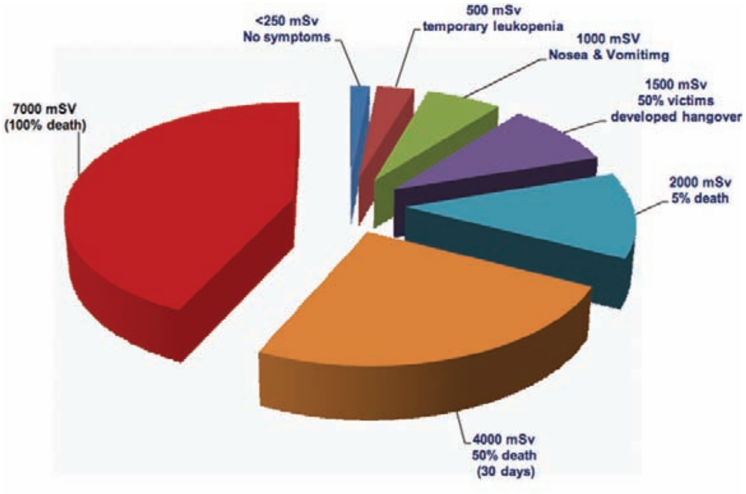


Figure 3. Acute radiation syndrome Vs radiation dose and death percentage.

fission reaction and prominent source of alpha emission that damage the biological systems of the personals engaged with cleanup operation[40-41].

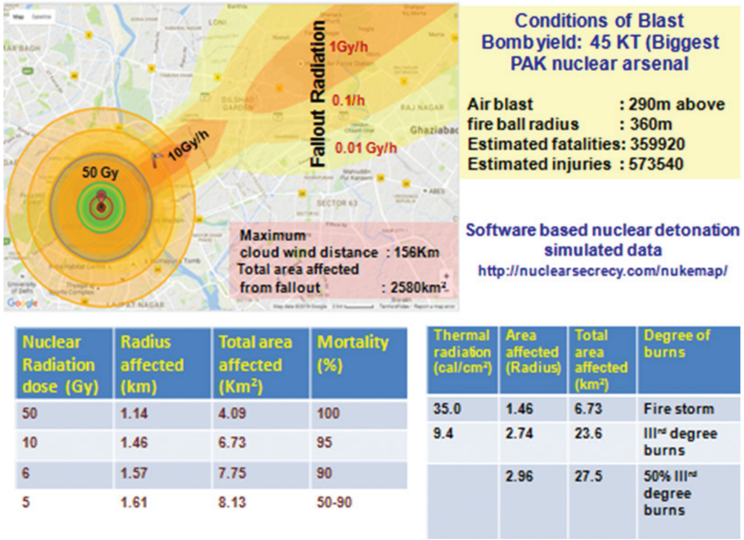
9. VIRTUAL COMPUTER SIMULATION ANALYSIS OF NUCLEAR WEAPON DETONATION VS RADIATION DOSE IN THE ENVIRONMENT

Software based simulation[42] predicted the possible nuclear weapon devastating effect in terms of nuclear radiation yield, thermal radiation and blast/shock wave strength along with increasing time and distance variables. Data of the 45KT yield nuclear bomb detonation computer based simulation was predicted maximum radiation dose (neutron+gamma ray+alha+beta) to be 50 Gy within the radius of 1.14 km. However, with increasing distance, radiation dose will be reduced as it will be 10 Gy at 1.46 km radius, 6 Gy at 1.57 kn radius and 5 Gy at 1.61 km radius. Though, radiation dose will be 10 Gy in the radius of 1.46 km however, thermal radiation produce fire storm within this radius, therefore, everything come in contact with firestorm will be meltdown. Therefore, medical intervention cannot be a viable option in the short hypocenter area. Further, 7 km - 8 km distance from the hypocenter will have 5-6 Gy of radiation, however, third degree burns will be the main culprit of instant deaths. Therefore, more causality will occur due to heat burns as compared to radiation injuries. Instead of initial first cycle of radiation, residual radiation due to radionuclide's fallout will be the major concerned for evacuation workers. Fallout contour (Fig. 4) demonstrated ~10 Gy/h radiation dose due to fallout within the area of 15.6 km^2 with maximum stem of 1.37 km. The radiation level will be about 1 Gy/h at maximum downwind cloud distance of 39.8 km with maximum width of 2.83 km. The total affected area will be about 200 km. Similarly, the radiation level in the next 83.9 km will be 0.1 Gy/h with maximum width of 7.63 km. The approximately affected area of 0.1 Gy/h radiation dose will be approximately 729 km^2. Further calculation revealed that total area affected with low radiation level equal to 0.01 Gy will be 2580 km^2. Considering the simulated data for possible interventions of medical countermeasure is only applicable in the fallout area having high radiation background (0.1 Gy/h to 10 Gy/h) without sufficient heat radiation[42]. However, in real scenario combined (radiation with heat) injuries will be the real threat. Therefore, strategies to manage combined radiation injuries need to be developed.

10. BIOLOGICAL RADIOPROTECTOR DEVELOPMENT

In view of above mentioned planned or unplanned radiation incidents/accidents, development of radioprotective agents is considered as an urgent requirement. Since 1945, several radiation countermeasure agents from natural and synthetic origins are evaluated for their efficacy, toxicity and utility. Based on the technical knowledge and scenario of applications, radiation countermeasures are classified into three main categories i.e. radioprotectors, radiomitigators and radiation-therapeutics. Radioprotectors are agents which administered before radiation exposure to protect the radiation damage. Radiation mitigators are the compounds that administered shortly after radiation exposure but before radiation exposure symptoms manifested. While, radiation-therapeutics are classified as the agents which given after ARS symptoms appeared. These agents basically acts to stimulate repair or regeneration in the damage biological system. To develop excellent, ideal radiation countermeasure agents, various idealistic properties were primarily proposed by the investigators from AFRI, USA and now followed to test the efficacy, toxicity and applicability of the radioprotective agents in different emergency scenario at global scale. Some of the ideal consensus parameters for radioprotector development are as follows:

- A radiation countermeasure agent should provide multifaceted protection to all biological systems against lethal doses of ionising radiation despite different



Conditions of Blast
Bomb yield: 45 KT (Biggest PAK nuclear arsenal

Air blast : 290m above
fire ball radius : 360m
Estimated fatalities: 359920
Estimated injuries : 573540

Maximum cloud wind distance : 156Km
Total area affected from fallout : 2580km^2

Software based nuclear detonation simulated data
http://nuclearsecrecy.com/nukemap/

Nuclear Radiation dose (Gy)	Radius affected (km)	Total area affected (Km^2)	Mortality (%)
50	1.14	4.09	100
10	1.46	6.73	95
6	1.57	7.75	90
5	1.61	8.13	50-90

Thermal radiation (cal/cm^2)	Area affected (Radius)	Total area affected (km^2)	Degree of burns
35.0	1.46	6.73	Fire storm
9.4	2.74	23.6	IIIrd degree burns
	2.96	27.5	50% IIIrd degree burns

Figure 4. Computer based simulation of nuclear weapon (yield 45KT) detonation and level of nuclear (instant and fallout radiation) and heat radiation with increasing distance.

sensitivity of different organs against radiation damage!!.

- A radioprotective agent should have nearly same efficacy for different types of radiation (X-ray, gamma ray, neutrons) and dose rate!.
- An agent that can provide extended protection over several days and can reduce effect of radiation by the factor of 2 (DRF 2.0 or more) without appearing toxic effects.
- An agent should not have cumulative effect if required repeated administration (for mitigator or therapeutic class of radiation countermeasure).
- An agent should have no/minimal adverse effects and toxicity on physiology and organ functions of treated subjects.
- An agent should have large effective time and dose window with extended stability profile.
- The agent should be compatible with the wide range of supportive care agents and drugs like antibiotics, immunotherapeutics etc.
- A radioprotective agent should have sufficiently long shelf life and economical viability.
- A radioprotector for emergency, should be effective in bear minimum time period (<30 min) and its effectiveness should be maintained for longer durations (>6 h).
- A radioprotective agent should have differential protection in normal and tumour cells/tissue, so that it can be used during normal radiotherapy. A radioprotective agent should be useful in combined radiation injuries scenario if possible.

Despite all serious attempts for radiation countermeasure development, till date not a single agent was qualified on all outstanding parameters advised to consider during the course of developmental stages. A number of radiation countermeasures (specifically radioprotectants and radiomitigators) have been identified and at various stages of US FDA approval (Table 2).

11. NATIONAL AND INTERNATIONAL STATUS OF RADIATION COUNTERMEASURE

Several chemical compounds of synthetic and natural origins have been tested for their radioprotective activity after world war II. In 1959, U.S. Army initiated a program at Walter Reed Institute to identify and synthesise drugs molecules capable of protecting individuals from gamma radiation. They synthesis approximately 4000 chemical compounds and tested their radioprotective efficacy. Among 4000 compounds screened, only amifostine (WR2721) was selected and further evaluated for its toxicity. This compound is still under clinical trial phase-III for neck and head cancer radiotherapy patient's normal tissue protection. However, due to its neurotoxicity i.e. nausea and vomiting it was not qualified for nuclear accidents medical management for general public. Since from 1959, hundreds of chemical and natural compounds have been evaluated for their radioprotective activities in USA and other parts of world including Europe and Russia. However, US scientists have taken lead in radiation countermeasure development[43-45] resulted eight molecules have been granted IND status and another four are under advance stage of development as shown in Fig. 5.

In India two main Centres i.e BARC Mumbai and INMAS, Delhi have initiated radiatioprotector development work almost two decades before and evaluated several molecules for their radioprotective activities. Particularly, INMAS took the lead in radiation countermeasure development programme and evaluated Indian herbs as the prominent sources of radioprotective molecules. *Podophyllum hexandrum*, *Hippophae rhamnoides*, *Rhodulla embricata* and *Tinospora cordifolia* was evaluated for their radioprotective efficacy [46-52]. Apart from that radioprotective efficacy of pure molecules isolated from *Podophyllum hexandrum* was established at INMAS[53]. Study on *pdophyllum hexandrum's* pure molecules is progressing towards higher animal efficacy and toxicity studies using NHP model. Another novel approach using radioresistant bacteria as prominent source of radioprotective molecules was undertaken at INMAS. A secondary metabolites of radioresistant bacterium *Bacillus* sp. INM-1 was isolated, characterised and evaluated for radioprotective activity in lower animal model[54-60]. The study is progressing well towards formulation development and toxicity evaluation. Besides INMAS, other Indian investigators also evaluated several Indian herbs for their possible radioprotective efficacy as shown in Table 1.

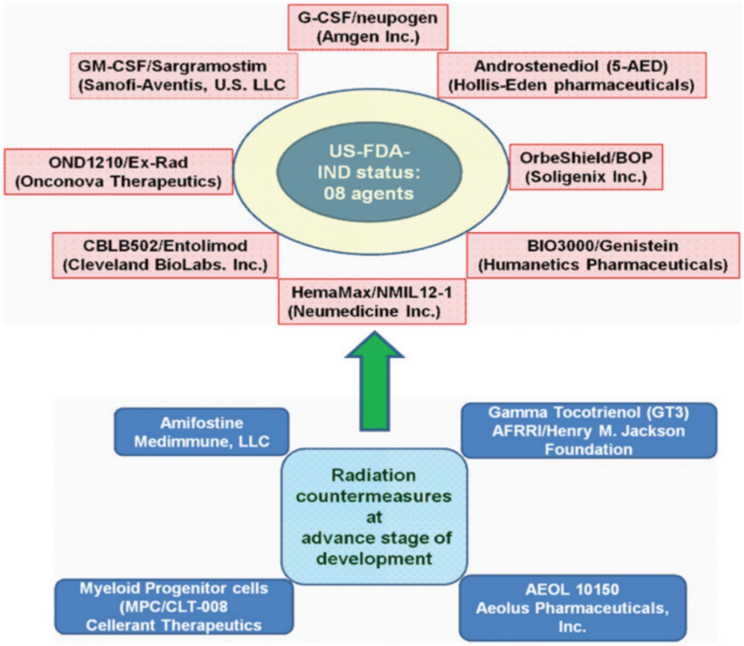
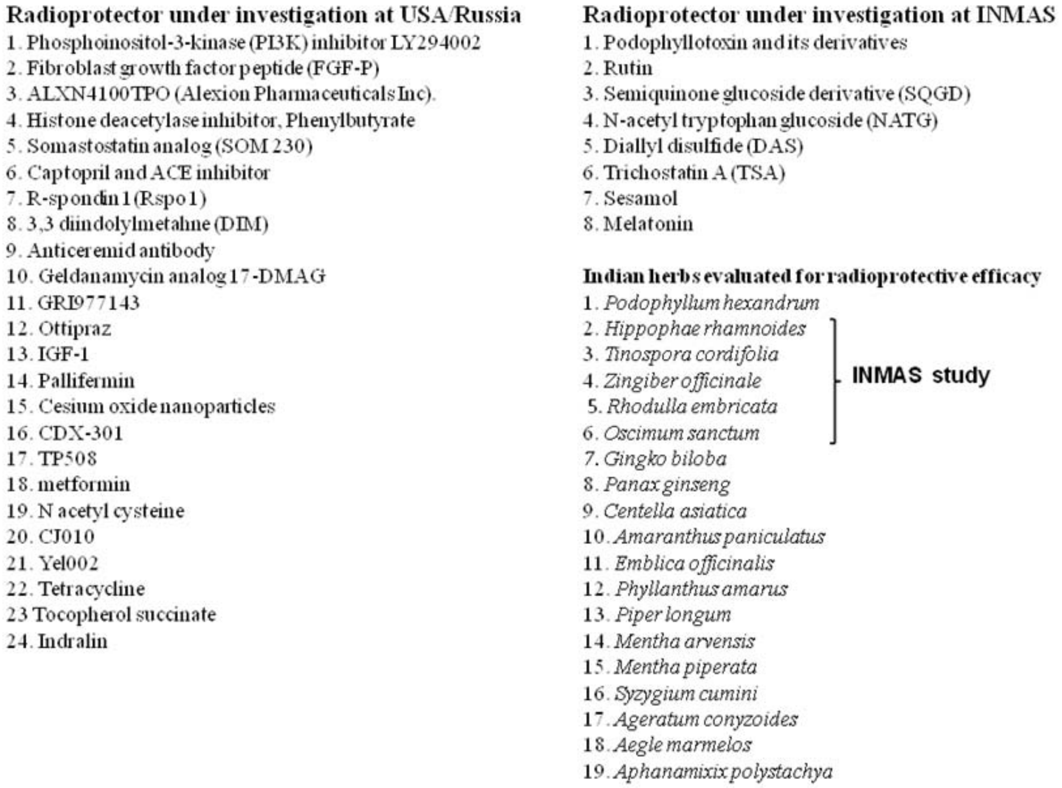


Figure 5. Radiation countermeasure in advance stage of development in USA.

12. CONCISE ROADMAP OF RADIATION COUNTERMEASURE DEVELOPMENT

Though, Drug Controller General of India (DCGI) do not have any specific guidelines under "Drug and Cosmetic Act of India" to evaluate and approve radiation countermeasures for clinical and emergency uses. However US-FDA formulated guidelines to evaluate and approve a radiation countermeasure for clinical testing. The radiation countermeasure development process was categorised in two parts i.e. i). Preliminary

Table 1. Radioprotective agents under investigation in USA/Russia and in India[42-45,46-60]



Radioprotector under investigation at USA/Russia

1. Phosphoinositol-3-kinase (PI3K) inhibitor LY294002
2. Fibroblast growth factor peptide (FGF-P)
3. ALXN4100TPO (Alexion Pharmaceuticals Inc).
4. Histone deacetylase inhibitor, Phenylbutyrate
5. Somastostatin analog (SOM 230)
6. Captopril and ACE inhibitor
7. R-spondin 1 (Rspo1)
8. 3,3 diindolylmetahne (DIM)
9. Anticeremid antibody
10. Geldanamycin analog 17-DMAG
11. GRI977143
12. Ottipraz
13. IGF-1
14. Pallifermin
15. Cesium oxide nanoparticles
16. CDX-301
17. TP508
18. metformin
19. N acetyl cysteine
20. CJ010
21. Yel002
22. Tetracycline
23 Tocopherol succinate
24. Indralin

Radioprotector under investigation at INMAS

1. Podophyllotoxin and its derivatives
2. Rutin
3. Semiquinone glucoside derivative (SQGD)
4. N-acetyl tryptophan glucoside (NATG)
5. Diallyl disulfide (DAS)
6. Trichostatin A (TSA)
7. Sesamol
8. Melatonin

Indian herbs evaluated for radioprotective efficacy

1. *Podophyllum hexandrum*
2. *Hippophae rhamnoides*
3. *Tinospora cordifolia*
4. *Zingiber officinale*
5. *Rhodulla embricata*
6. *Oscimum sanctum*

INMAS study

7. *Gingko biloba*
8. *Panax ginseng*
9. *Centella asiatica*
10. *Amaranthus paniculatus*
11. *Emblica officinalis*
12. *Phyllanthus amarus*
13. *Piper longum*
14. *Mentha arvensis*
15. *Mentha piperata*
16. *Syzygium cumini*
17. *Ageratum conyzoides*
18. *Aegle marmelos*
19. *Aphanamixix polystachya*

screening and selection of lead radioprotective compounds and II). Translational studies including preclinical and clinical aspects. Due to lack of consensus on common molecular target of radioprotection, no high throughput methods for screening of radioprotective agents are available. Ionising radiation induced free radicals in the biological system, therefore, free radicals scavenging potential of an agent considered as an integral part of its preliminary selection. Although, possessing antioxidant activity is not the sole criteria to select the lead compounds for radioprotection purpose. Several excellent antioxidant molecules like tampol, trolox, ascorbic acid, quercetin, lycopene etc. do not provide desirable *in vivo* whole body radioprotection and therefore discarded from the list of potential radioprotectors. Radiation exposure induced damage to bio-macromolecules i.e. DNA, protein and enzymes and thus impaired their functional integrity lead to cell death. Therefore, radioprotection to DNA, proteins and enzymes may be good criteria for radioprotector screening. Based on the outcome of *in vitro* and *ex-vivo* preliminary studies, selected compounds can be subjected to *in vitro* radioprotection assays using human or animal cells in culture. If selected agent provides desirable radioprotection against lethal/sub-lethal doses of gamma radiation to the cells in culture, the same can be subjected for whole body survival assay using lethally irradiated mice. Actually, whole body survival offered by radioprotective agent to the lethally irradiated mice is the gold standard for final selection of a radioprotective compound for further studies. If an agent is qualified *in vivo* radioprotection scale, than systemic level radioprotection studies need to be started. Systemic level radioprotection study comprises histological and biochemical and molecular analysis of vital organs. Based on the outcome of the preliminary studies, second phase i.e. translational phase need to be started. Drug's pharmacological target identification and validation are an integral part of second phase study. The next step of radiation countermeasure development as suggested by US-FDA is toxicological and safety pharmacological profiling of the drug candidate in GLP certified laboratory. If drug candidate qualify on toxicological and safety pharmacological parameters, it will be ready for higher animal (preferably non-human primate) testing. However, before initiating NHP studies, it is mandatory to develop a standardised formulation intended to be use in human trials. Further, due to ethical prohibition to irradiate human during clinical trials, US-FDA suggested to develop an efficacy biomarker specific to the drug's molecular action. The efficacy biomarker may correlate the animal efficacy dose corresponding to similar efficacy in human even without exposing the human subjects to gamma radiation. Followed by completion of non-human primate efficacy and toxicity studies with no or manageable adverse indications, radiation countermeasure agent will be ready for human clinical safety trial[61]. The whole procedure is highly expensive, time consuming and full of risks. The complete summarised schematic flowchart depicting all steps of radiation countermeasure development along with time scale is as given in Fig. 6.

13. SIGNATURE ISSUES, TECHNICAL GAPS AND COMPLEXITY IN RADIATION COUNTERMEASURE DEVELOPMENT

The area of radiation countermeasure development is full of challenges and technical complexities. Several issues which significantly affect the mortality and morbidity of radiation

Table 2. Excellence *vs* practical consideration for radiation countermeasure development

Excellence tried to achieve	Bottlenecks to achieve excellence	Strategically applicable and Practically Achievable Radioprotection (SAPARA)
A single radiation countermeasure agent that can be use for prophylactic, mitigative and therapeutic applications.	Difficult to achieve	Separate agent for radioprotection, mitigation and therapeutic applications should be developed.
A single radiation countermeasure agent for whole body protection	Protection efficacy of a radiation countermeasure will be differing with different types of radiation due to different RBE of different radiation types.	Separate agent should be developed for low LET and High LET radiation.
An efficacious radiation countermeasure against lethal dose of radiation	Efficacy level of a radiation countermeasure cannot be uniform in different subjects. Like, efficacy may be varied in male to female, young to adult and children to old age persons.	Though, lethal exposure is real but a rare threat while, sub-lethal and below sub-lethal irradiation exposure is equally fatal. Thus, sub-lethal radiation exposure should be considered potential threat for civil population.
Radiation countermeasure to manage nuclear reactor accidents	The maximum radiation dose in the surrounding area of world worst nuclear accidents i.e. Chernobyl and Fukushima (level 7) was observed to be in the order of 100-678 mSv for public. Interestingly, 500 mSv is the international allowable short-term dose for emergency workers. However, in both accidents, the reactor employees who were working in the vicinity of the reactor, exposed to whole body 2-20 Gy dose of mixed radiation and died within weeks.	Though no specific radiation countermeasure intervention will be required to the general public who exposed less than 500 mSv dose of radiation. However, radiation worker exposed with high dose (2-20 Gy) of radiation definitely required radiation countermeasure (mitigator/therapeutics) with supportive care including antibiotics and immuno-stimulants.
Applicability of radiation countermeasure during deliberate nuclear eventuality	The dose of nuclear radiation during Hiroshima and Nagasaki atomic attack was very high (neutron+gamma) at hypocenter but reduced significantly beyond the 1000 m. Interestingly, due to extreme heat radiation within 1000 m everything was meltdown. So, no physical, chemical, biological or medical intervention will be helpful within 1000m hypocenter radius.	Beyond the 1000 m distance, radio mitigators and radiotherapeutic will be required. Further, medical management of radiation combined injuries (Radiation+heat burns+shock wave injuries) should be the prime concerned to manage the atomic attack.
Radiation countermeasure to handle nuclear fallout and secondary radiation after nuclear accident or bomb detonation	Past nuclear accidents suggested that Iodine-131 is the major threat (half life 8h) which release in gaseous phase and accumulated in the thyroid gland of animals and human and caused localized radiation damage.	Cleanup operation in the contaminated area will be initiated after proper monitoring of the radiation level. The radiation level will be reduced substantially in the contaminated area with increasing time and distance. So a radio protective drug able to protect even sub-lethal doses of gamma/neutron radiation may be useful.
Applications and significance of radiation countermeasure for high doses (>6-50 Gy) of radiation	The high dose radiation exposure possibilities lies with the uranium enrichment plant incidents, overexposure during radiotherapy, nuclear submarine accidents and occupational workers directly engaged with the nuclear reactor accident (>6 level).	High dose radiation exposure scenario only allows the application of radiation mitigators and therapeutics to manage the ARS in radiation victims.
Radiation countermeasure for human-space mission in future	NASA's curiosity mission was calculated the total galactic radiation absorbed during 360 days return trip to the MARS i.e. 662+/108 mSv.	662+/108 mSv exposure is far below from the upper limits of accepted dose for an astronaut career. European, Russian, and Canadian Space Agencies were decided exposed radiation dose limit upto 1000 mSv for astronaut. While, NASA limits are between 600-1200 mSv. Therefore, radioprotective drug able to neutralize at least 1000 mSv (1Gy) radiation effect will be sufficient for future MARS men exploration. Though radiomitigators and radiotherapeutic agents may also be useful for MARS colonizers.

exposure are still not answered technically. Some of them are discussed as follows:

- Radiation effects on biological systems depend on the radiation source strength (dose rate) and total absorbed dose in particular system/organ. The radioprotective efficacy of radiation countermeasure agent deviates significantly with changing radiation dose rate. Therefore, radioprotective efficacy of a radioprotector may differ with different dose rate. There is no standard way to fix this issue. However, 0.6Gy/min radiation dose rate was considered optimum at AFRRI to evaluate radioprotective efficacy of a drug molecule.

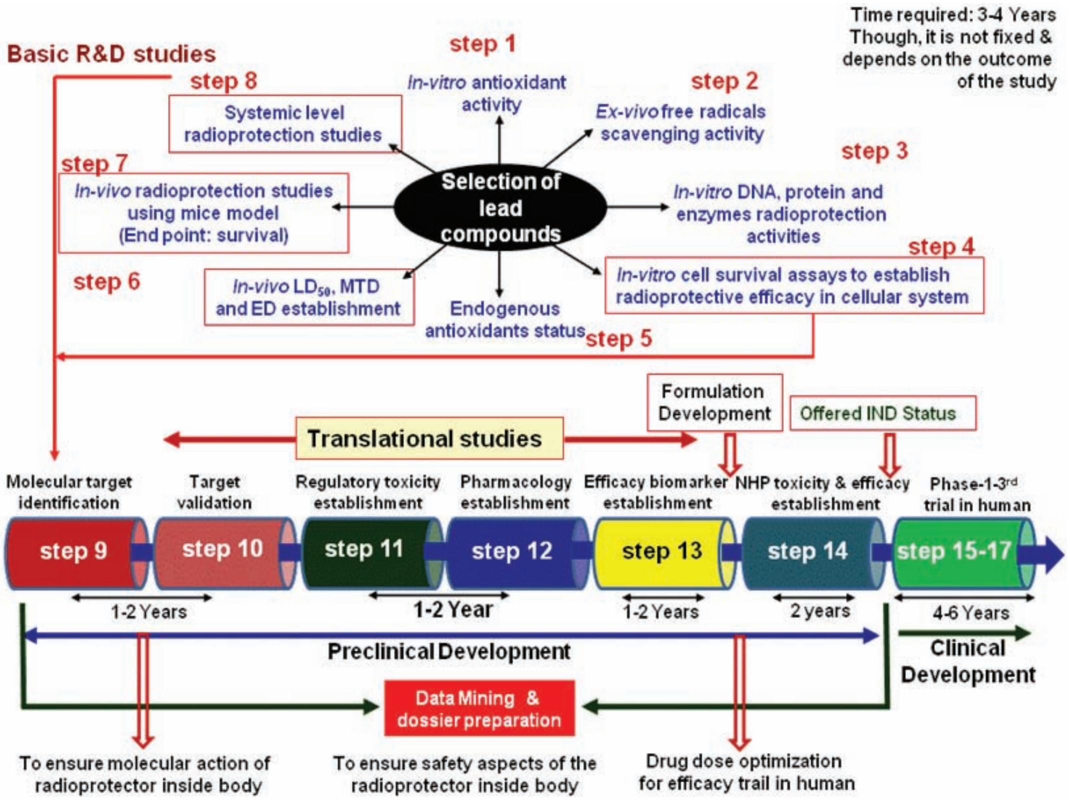


Figure 6. A roadmap to develop radiation countermeasure for human applications.

- Nuclear emergency situation involved mixed radiation threat. Different types of radiation have different energy strength and therefore varied biological damage. Mixed radiation environment includes neutron, gamma rays, alpha particles, beta particles, fission product, heavy nuclei, muons, protons and charged ions. According to ICRP report, Radiation weighting factors W_R i.e. Relative biological effectiveness (RBE) is substantially differs with different types of radiation. For examples, X-rays, gamma rays, beta particles, muons have W_R equal to 1. Neutron radiation (< 1-50Mev) have W_R 2.5-5.0, protons and charged pions have W_R 2, while, alpha particles, nuclear fission products and heavy nuclei have W_R of 20. Due to wide variation in $W_{R,}$ radioprotective efficacy of a radiation countermeasure may not be equal for all radiation types.
- Different organs of the body have variable radiosensitivity. Immune system is more radiosensitive while CNS does not. Therefore, radiation doses which do not induced significant damage to skin, muscles and CNS, may be fatal for bone marrow, GI system and eyes. Therefore, common drug may not protect all biological systems against radiation damage. Unavailability of high-throughput method for human radio-biodosimetry and triage further complicate the medical management of ARS in radiation exposed personals.
- Despite several efforts worldwide, there is no specific biochemical radiation biomarker was identified that can be used to evaluate radioprotective efficacy of radiation countermeasure agents.
- Complex nature of combined radiation injuries (radiation+heat burns+traumatic shock wave damage) will be the real scenario in case of nuclear eventuality. However, no specific experimental animal model is available that can be used to evaluate radiation countermeasure efficacy against combine radiation injuries.

14. RECOMMENDATIONS

Lack of specific cellular or molecular targets, unacceptable toxicity of countermeasure agents at efficacious dose, less effectiveness of the agents against different types of radiation, less interest of pharmaceutical industries in radiation countermeasure development and unclear regulatory guidelines complicate the radiation countermeasure development programme. Despite several problems, investigators are still working to develop radiation countermeasure worldwide. Keeping the entire variable in consideration following recommendations are being suggested to expedite the 'strategically applicable and Practically Achievable Radioprotection (SAPARA) principle:

- Definition of excellence should be modified according to the applicability of radiation countermeasure. So that unrealistic hurdles can be avoided.
- Strategic requirements and usable scenario of radiation countermeasure should be clearly defined (Table 3).
- Radiation dose of 5-6 Gy is considered lethal for human. However, probability of general public exposure to that much of high dose of radiation is very rare. Even during nuclear accidents and nuclear attack in Japan, general population inhabited at the distance >1.5 km^2 do not

Table 3. Probable selection criteria of radiation countermeasure (protector, mitigator and therapeutic agents) applications in different emergency situations

Radiation accidents	Radioprotector	Radiation mitigators	Radiation therapeutics
Nuclear reactor accidents (> level 7)			
Workers operating at the site of accident	X Radiation dose: > 10 Gy at the core of the reactor	✓	✓
General public at distance (2 km^2)	✓ (>1-2 Gy)	✓	✓
Fallout radiation in contaminated area	✓ < 500 mSv	✓	✓
Cleanup operation	✓	✓	✓
Nuclear attack (45 KT yield)			
Detonation hypocenter and surrounded radius of about 4-6 km^2	X 10-50 Gy but heat radiation burn everything	X	X
Radiation dose within 7-8 km^2 radius (dose 5-6 Gy)	X Instant exposure so no time for radioprotector action	✓ With 3rd degree burns (combined radiation injuries management	✓ With 3rd degree burns (combined radiation injuries management
Fallout in approximately 2580 km^2 area	✓ Radiation dose: 0.01 to 1 Gy/h	✓	✓
Iodine-131 accumulation in thyroid gland of exposed human	✓ KI tablet	✓ Decorporating agent	✓
Contamination cleanup activity	✓	✓	✓
Radiation accidents in Military sector like nuclear submarine accidents			
Nuclear sub-marine accidents Radiation dose: 5-10 or more radiation)	✓ Low time window agents	✓ Agent able to protect gamma+Neutron radiation	✓
Uranium enrichment and uncontrolled criticality reaching accidents	X 20-30 Gy instant exposure	✓ Agents able to protect combined radiation injuries (Radiation +3rd degree heat burns	✓ Immuno-modulatory agent to regenerate immune system
Medical sector radiation overexposure			
Over radiation exposure during Radiotherapy and fluoroscopy	✓ Very much applicable to protect normal tissue from radiation damage.	✓ Can be used in case of over radiation exposure due to miscalculated radiation dose delivery (human or machine error)	✓ Can be used during recovery period
Radiation incident due to dismantling of radiation source in scrapyard			
Several incidents have been reported at global scale in which peoples exposed with lethal radiation doses during dismantling of old irradiators	X Due to involvement of unskilled labourer in the dismantling work, no prior information will be dissipated for probable radiation threat	X Most of the cases are come in light after Acute radiation syndrome start to appear in exposed persons. So radiation mitigator will not be applicable in this scenario.	✓ Radiation therapeutics is the only choice of medical treatment of the radiation victims.

Note: X: Not applicable; ✓: Applicable

expose with even sub-lethal doses of gamma or neutron radiation. Therefore, radiation countermeasure for general public protection during emergency situation is more than sufficient if it can effective against sub-lethal (2-3 Gy) doses of gamma/neutron radiation.

- Combined radiation injuries will be the real scenario during nuclear explosion. Therefore, a radiation counter measure able to help in recovery from heat burns and shock trauma will certainly be an ideal agent.
- Several nuclear submarine accidents have been documented in the past. The submarine contingent operates in close proximity of nuclear reactor on board. Thus, chances of radiation exposure are very high in case of nuclear submarine. Therefore, fast acting radioprotective (low time window), mitigative agent able to protect from lethal to supra lethal (5-10 Gy) doses of mixed radiation (gamma+neutron) will be necessary for submarine contingent.

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He has contributed to improve the final contents of the present review. He also provided his valuable suggestions to make this review article as simple as a non-technical person of limited scientific background can understand the problems associated with radiation countermeasure development and possible solutions to combat radiation emergency effectively.