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(54) **USE OF MULTIPLE ANTIOXIDANT MICRONUTRIENTS AS SYSTEMIC BIOLOGICAL RADIOPROTECTIVE AGENTS AGAINST POTENTIAL IONIZING RADIATION RISKS**

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See application file for complete search history.

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(57) **ABSTRACT**

Disclosed herein is a method for protecting humans in need of such protection from physical damage caused by ionizing radiation comprising administering to said humans on a defined basis prior to and after exposure to such radiation a plurality of antioxidants at a dosage level directly proportional to the radiation level likely to be encountered.

7 Claims, No Drawings

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USE OF MULTIPLE ANTIOXIDANT MICRONUTRIENTS AS SYSTEMIC BIOLOGICAL RADIOPROTECTIVE AGENTS AGAINST POTENTIAL IONIZING RADIATION RISKS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the use of antioxidants to reduce the effects of radiation on humans.

2. Description of Related Art

Ionizing radiation (X-rays and gamma rays) has proven to be a double-edged sword in clinical medicine since its discovery by Dr. Wilhelm Roentgen in 1895 (1, 2). Energy wavelength progresses along the electromagnetic continuum from longer ranges (radiowaves, microwaves, infrared, heat waves) to medium wavelengths (visible light, ultraviolet light) to shorter wavelengths (ionizing radiation, e.g., x-rays and gamma rays). It is these x-rays and gamma rays that are able to drive electrons out of their normal atomic orbits with enough kinetic energy to generate charged molecules (including free radicals) that damage cells. In addition to the initial realization by the medical community that ionizing radiation could detect as well as treat human diseases, came the unfortunate demonstration that it could also induce serious illness.

In fact, most of the ionizing radiation to which the human population is exposed, other than that received from environmental sources, is from the diagnostic and screening imaging machines employed by today's clinical healthcare professionals. For example, in the past, x-ray-induced skin cancers were noted with higher frequency in radiologists. Obviously, whenever x-rays are employed, it is done with caution so that patients and healthcare providers are exposed to as low a dose as possible. Physicists and nuclear engineers have devised improved equipment and radiation beam delivery systems to reduce the level of diagnostic radiation dose without compromising the quality of images. However, radiation biologists agree that there is no threshold dose below which there is no risk of cellular damage. In fact, even a single radiation track that crosses a cellular nucleus has a very low, but finite, probability of generating damage that may result in cellular dysfunction, structural mutations, and subsequent genetic implications.

While most clinical radiologists believe the risks of x-ray exposure are very small, residual biologic effects from alteration in structure are dependent on whether the cell repairs its injured components. Although the vast majority of damage is repaired, some may be unrepaired or misrepaired and therein lies the problem. In adults, most radiation researchers consider cancer induction to be the most important somatic effect of low dose ionizing radiation and this outcome may occur in nearly all the tissues of the human body. Academic radiologists are also raising future disease concerns regarding pediatric age groups because of the increased numbers of imaging studies now being performed in younger populations (3). In light of these concepts, the healthcare profession states that ionizing radiation exposure should only occur when there is a defined healthcare benefit, or indicated when the risk-benefit ratio is favorable to the patient. The critical concept has been always to protect humans by physical local factors, such as shielding and decreasing doses and x-ray times. However, no one has previously considered the additional aspects related to a strategy of systemic biological protection.

Recent advances in imaging technology have made possible the detection of many illnesses such as heart disease, cancer, neurologic diseases, arthritis and other acute or chronic conditions. It is also a significant development that this technology may detect the problem at an early stage when treatment interventions allow for less invasive therapeutic

procedures and/or surgical operations and yet achieve improved health outcomes. In this environment, the number of diagnostic x-rays performed is truly enormous. It was estimated in the United States for the period 1985 to 1990 at least 800 diagnostic studies per 1,000 population were performed and this excluded dental x-rays and nuclear medicine (4). The importance of these findings can be appreciated since it is probable that frequent low dose radiation exposures may be more damaging than a single higher dose exposure on the criteria of gene mutations and cancer promotion.

The current era has seen an explosion of diagnostic imaging equipment including the introduction of computed tomography, digital radiography, expanded nuclear medicine applications, interventional radiology, and lengthening fluoroscopic procedures. In concert with these technical innovations, the concept of early disease detection and screening large populations to employ illness prevention strategies will generate further rapid expansion of members of imaging studies with increased ionizing radiation exposure to the public. As a direct consequence of this new proactive healthcare approach, imaging will be performed in many more, otherwise healthy, people and asymptomatic "at risk" populations. In addition, initial exposures will occur at an earlier age and the mandate of serial follow-up imaging will result in an overall greater frequency of x-ray studies.

The doses of ionizing radiation exposure in imaging studies vary dramatically from less than 0.1 rem (1 millisievert, mSv, for x-rays and gamma rays, 1 rem=1 rad) per test for some procedures to others that involve levels in some organs in excess of 25 rem per test. Table 1 lists a sampling of common studies (5-8). Note that while the red marrow dose is usually the reported "standard," the actual target organ dose is actually often significantly higher. For example, mammography exposes the actual breast tissue to approximately 700 mrem, virtually equal to the total skin entrance dose. Likewise, thallium scanning exposes the thorax to approximately 1000 mrem, about 20 times the red marrow dose.

TABLE 1

Procedure	Effective Dose Equivalent (HE)		Skin Entrance Dose
Diagnostic X-ray	mSv*	mrem	mrem
Chest AP, 100 kVp	0.015	1.5	10
Lumbar spine AP, 80 kVp	0.273	27.3	359
Upper G.I.	4.1	410	2300/min
Coronary angioplasty	50–150/min	5000–15000/min	25000/min
Head CT	0.8–5	80–500	4500
Abdomen CT	6–24	600–2400	2000
Dental	0.01	1	350
Electron beam CT heart	0.14–0.3	14–30	150
Mammogram	**	**	700
Nuclear Medicine	mSv	mrem	mrem
18F-Fluorodeoxyglucose, 10 mCi	9.99	999	NA
99 mTc-MAA Lung scan (perfusion only) 5 mCI	2.03	203	NA
99 mTc-HDP Bone scan 20 mCi	5.92	592	NA
201Tl Thallium scan 3 mCi	25.53	2553	NA

*Seivert is the official international unit of biological radiation dose. One Sv = 100 rem.
ND = Data not available
** = Dose negligible
NA = Not applicable

Depending on the age of the individual, frequency of testing, exposure time, and total dose, the diagnostic or screening imaging studies could increase the risk of somatic damage (some forms of cancer such as leukemia, breast, and thyroid) as well as genetic damage (such as with gonadal exposure) in the target population. In fact, radiation experts are beginning to call for special attention to issues of exposure from CT Scanning in younger patients (9). It should be emphasized that the risk of radiation injury produced by diagnostic doses below 0.5 rem is very small in comparison to other agents that are present in the diet or the natural environment. However, regardless of the "insignificant" risk with any individual exposure or imaging event, the total effects of ionizing radiation are on-going, cumulative over time, have the potential for lifelong expression, and may have a future generational genetic impact.

It should be anticipated that as more sophisticated imaging studies are available for diagnosis and screening, the individual small risks may add up over a lifetime. For example, nuclear medicine has been expanded to new techniques which include intravenous systemic injection of radionuclides and expose various body organs to differing radiation doses (10). The recent impact of interventional techniques often combined with surgical procedures also increases the imaging risks. Furthermore, advanced fluoroscopic imaging used for technical procedures such as percutaneous transluminal angioplasty, transhepatic cholangiography, stent and drainage placements, as well as venous access procedures may involve significant radiation exposure (11). In fact, by the year 2000 in the United States alone, about 750,000 patients underwent coronary balloon angioplasty (12). Finally, the most recent technical innovations utilized in screening procedures, such as spiral and electron beam computed tomography for heart, lung, colon, and total body scanning are new clinical areas where issues of radiation dosimetry have to be considered (13, 14).

Currently, the FAA and airlines consider flight personnel (including flight attendants) as radiation workers. As such, they are allowed a regulatory dose limit 50 times the dose limit allowable to the general public. According to recent estimates, over 400,000 frequent fliers travel over 75,000 air miles each year, which means that they will exceed radiation dose limits to the general public from galactic (cosmic) radiation during flight (15). The radiation exposure during flight varies with altitude, flight time, air route, and solar flare activity. As an example, a routine flight from New York to Chicago (highest altitude 37,000 feet) yields a radiation dose rate of 0.0039 mSv per block hour. (The block hour begins when the aircraft leaves the blocks before takeoff and ends when it reaches the blocks after landing.) A flight from Athens, Greece, to New York (highest altitude 41,000 feet) yields a radiation dose rate of 0.0063 mSv per block hour. The total radiation dose form the New York to Chicago route is 0.0089 mSv and the Athens to New York flight is 0.0615 mSv. For reference, the annual exposure limit for the general public is 1 mSv. The only remediation recommended by the FAA for radiation exposure during flight is to limit flight and avoid traveling during periods of increased solar flare activity. Airline crew members flying long-haul high-altitude routes receive, on average, greater exposures each year than do radiation workers in ground-based industries where radioactive sources or radiation-producing machines are used (16).

The United States military is aware of and concerned about potential radiation exposures to our troops. Perhaps the most obvious population at risk in the military are pilots flying long, high-altitude missions. The expected radiation doses would be in accordance with the estimates outlined above. The most recent U.S. Army study on the issue recognizes four nuclear radiation exposure risk categories of military personnel based on their likelihood and extent of exposure (17, Table 2). The Army currently has three radiation protection programs to address these risk categories. One is applied to those individuals whose duties parallel those of civilian radiation workers. These include military personnel, such as x-ray technicians, radiologists who do radiological examinations, researchers who use radionuclides, and technicians who maintain radioactive commodities, such as radiation detection instruments and calibration sources. The second applies to soldiers whose primary occupation does not usually expose them to radiation. These are soldiers who might respond to a military situation, such as that covered by Allied Command Europe Directive (ACE) 80-63, in which radiation is present, but at doses not exceeding 700 mSv. The third category applies to those situations involving extremely high radiation exposure, such as nuclear war.

TABLE 2

Revised, Low-Level Radiation Guidance for Military Operations

Total Cumulative Dose[a]	Radiation Exposure State Category	Recommended Actions	Increased Risk of Long Term Fatal Cancer[b]
<0.5 mGy	0	None	None
0.5–5 mGy	1A	Record individual dose readings Initiate periodic monitoring	1:4,000
5–50 mGy	1B	Record individual dose readings Continue monitoring Initiate rad survey Prioritize tasks Establish dose control measure as part of operations	1:400
50–100 mGy	1C	Record individual dose readings Continue monitoring Update survey Continue dose-control measures Execute priority tasks only[c]	1:200
100–250 mGy	1D	Record individual dose readings Continue monitoring Update survey Continue dose control measures Execute critical tasks only[d]	1:80
250–700 mGy	1E	Record individual dose readings Continue monitoring Update survey Continue dose control measures Execute critical tasks only[d]	1:30

[a]The use of the measurement millisievert is preferred in all cases. However, due to the fact that normally the military has only the capability to measure milligray (mGy), as long as the ability to obtain measurements in millisievert is not possible, U.S. forces will use milligray. For whole body gamma irradiation, 1 mGy is equal to 1 mSv. All doses should be kept as low as reasonably achievable (ALARA). This will reduce the

risk to individual soldiers and will retain maximum operational flexibility for future employment of exposed soldiers.

[b]This is in addition to the 1:5 and 1:4 incidence of fatal cancer among the general population. Increased risk is given for induction of fatal cancer (losing an average of 24 years of life for personnel ages 20-30 years). It must be noted that higher radiation dose rates produce proportionately more health risks than the same total dose given over a longer period.

[c]Examples of priority tasks are those missions to avert danger to persons or to prevent damage from spreading.

[d]Examples of critical tasks are those missions required to save lives.

This study committee made four recommendations:

1) When making decisions, commanders should consider the long-term health effects that any action may have on their troops. This recommendation was extended such that it became standard operating policy.
2) The U.S. Department of Defense should develop and clearly express an underlying philosophy for radiation protection. Specifically, the committee suggested,

a: application and adaptation of the system recommended by the International Commission of Radiological Protection,

b: in peacetime or nonemergency situations, soldiers should be accorded the same level of protection accorded civilians, and

c: in settings in which an intervention is required and specific numerical dose limits are neither applicable nor practical, commanders should justify the mission (there is more benefit than risk), examine competing risks, and optimize the mission (identify ways to minimize dose without jeopardizing the mission).

3) Military personnel should receive appropriate training in both radiation effects and protection. Their training will need to vary on the basis of the particular level of potential exposure and the task at hand.
4) A program of measurement, recording, maintenance, and use of dosimetry and exposure information is essential.

The programs, once again, include no protection measures other than controlling time, distance, and physical shielding.

Radiation workers experience a broad spectrum of working conditions that have radiation exposure as a normal part of the workplace environment. Examples include medical radiology workers, nuclear power plant workers, and workers who use radiation and radioactive materials in research. As mentioned above, commercial flight crews are also considered to be radiation workers. Owing to this occupational classification, radiation workers are allowed to receive 50 times the radiation dose allowed to the general public. Radiation workers also differ from the general public in that they receive training about the risks of radiation exposure and are monitored for their radiation exposure as part of their working paradigm. The nuclear regulatory commission (NRC) has established occupational dose limits as noted previously and procedures for monitoring and record-keeping. These standards and regulations rely solely on time, distance, and physical shielding as methods of radiation protection.

SUMMARY OF THE INVENTION

If it could be possible to devise a strategy to reduce the potential adverse effects of radiation exposure, it certainly seems reasonable that this approach should be undertaken regardless of how small the actual risk of injury might be. Federal law by regulatory code (C.F.R. 21 and C.F.R. 35) emphasize ALARA guidelines as they relate to occupational radiation exposure. This concept should be extended to the biological consequences of the doses received by all classes of exposed individuals, including patients. The guidelines could be referred to as DALARA (damage as low as reasonably achievable), whereby both the dose and its harmful consequences could be minimized without interfering with the efficacy, ease, or cost of diagnostic procedures, or occupational and other activities. This novel concept, supported by extensive data, is based on reducing radiation-derived free radical damage by antioxidant supplementation. Special attention needs to be given to population groups under chronic risk situations like frequent fliers, radiation workers, flight crews, and military personnel in combat theatres of operation. In these cases, episodic dosing with antioxidants is not adequate to achieve ALARA principles. These population groups should achieve and maintain higher antioxidant loads than persons with little or no expectation of radiation exposure.

In accordance with the present invention, twice daily dosing with a properly designed multiple antioxidant formulation is employed to maintain desired antioxidant loads in the body.

When chronically exposed (or chronic risk of exposure) individuals can be reasonably expected to incur an acute exposure, such as dangerous combat missions or any flight operations, they should supplement their regular antioxidant regimen with additional doses of selected antioxidants to protect against the anticipated exposure.

More particularly, the present invention is directed to a method for protecting humans in need of such protection from physical damage caused by ionizing radiation comprising administering to said humans on a defined basis prior to and after exposure to such radiation a plurality of antioxidants at a dosage level directly proportional to the radiation level likely to be encountered.

DETAILED DESCRIPTION OF THE INVENTION

Although brief medical x-rays themselves may not cause detectable damage, serial imaging, future screening studies (the importance of which cannot be currently predicted), flight exposures, military operations exposures, occupational exposures, and other factors, such as diet, disease status, and environmental exposure, and the like, may be clinically significant.

Relevant findings from basic scientific studies underscore this clinical concern. For example, a dose of 2 rem does not cause detectable mutations in normal human lymphocytes in culture. However, if the cells are irradiated with the same dose and treated with caffeine for a few hours after radiation exposure, an increased rate of cellular mutations is observed (18). This suggests that radiation-induced changes could be repaired in the normal course of events, but that subsequent exposure to caffeine impairs this normal cellular protective mechanism. In addition, a radiation dose that by itself would not be sufficient to induce cancer in an in vitro experimental system is able to do so in the presence of tumor promoters, such as phorbol ester, estrogen, and others (19-21). Furthermore, x-rays increase the incidence of cancer in cell culture by several fold when combined with chemical carcinogens, certain DNA viruses, ultraviolet radiation, or ozone exposure (22-26). Clearly, the potential hazard of even small radiation doses should not be ignored, since the target population readily interacts with agents present in the diet and environment, as well as other factors present in individual lifestyles.

Risk Categories

The following risk categories are general guidelines only and refer to acute exposures. The examples listed are not totally inclusive. The actual risk for any particular person may be modified by age and health status. The actual designation for all persons should be determined by healthcare or radiation physics professionals.

Population groups experiencing chronic radiation exposure risk, such as radiation workers (including commercial and military flight crews and field combat personnel), should maintain a higher baseline antioxidant load by taking a multiple antioxidant formulation (SEVAK) two times a day. They should then take the appropriate radioprotective formulation when the acute risk of exposure is expected (daily if necessary). Categories 2-4 are equivalent with respect to formulation and can be regarded to be adequate for exposures less than 15 mSv effective dose when taken on a daily basis along with SEVAK. The categories vary with respect to dose schedule when used for acute exposures only.

Category 1: Effective Dose 0.5 mSv or Less

For example: chest x-ray, dental x-ray, abdominal x-ray, skeletal plain films, most commercial flight passengers.

Category 2: Effective Dose 0.5-5 mSv

For example: diagnostic/screening computed tomography, urologic imaging, mammography, flight crews (commercial and military) and other radiation workers.

Category 3: Internal Radionuclide Exposures

For example: radionuclide imaging.

Category 4: Effective Dose 5-15 mSv

For example: limited diagnostic fluoroscopy (upper GI series, cholangiography, barium enema).

Category 5: Effective Dose Greater Than 15 mSv-250 mSv

For example: prolonged fluoroscopy/interventional radiology (coronary angiography, cerebral angiography, transluminal angioplasty) and some military personnel in combat operations (ground troops and seamen).

Category 6: Effective Dose 1000-2000 mSv

For example: radiation workers, civilian populations at risk near nuclear reactor sites, and at risk military personnel in overseas theatres of operation.

Category 7: Effective Dose Greater Than 2000 mSv (not Exceeding Bone Marrow Syndrome Doses)

For example: radiation workers, civilian populations at risk near nuclear reactor sites, and at risk military personnel in overseas theatres of operation.

Hereinafter, the term "imaging study" will be employed to include chest x-ray, dental x-ray, abdominal x-ray, skeletal plain films, diagnostic/screening computed tomography, urologic imaging, mammography, radionuclide imaging, limited diagnostic fluoroscopy, prolonged fluoroscopy/interventional radiology, and the like.

Baseline Formulation (SEVAK)
(Daily dose is contained in 4 capsules. Normally used for personnel in categories 6 and 7 and for personnel in category 2 who are member of flight crews and radiation workers.)

Vitamin A (palmitate)	5,000 I.U.
Beta-carotene (from natural *D. salina*)	15 mg
Vitamin D-3 (cholecalciferol)	400 I.U.
Natural source Vitamin E	
(d-alpha tocopherol)	100 I.U.
(d-alpha tocopheryl acid succinate)	100 I.U.
Buffered Vitamin C (calcium ascorbate)	500 mg
Thiamine mononitrate	4 mg
Riboflavin	5 mg
Niacinamide ascorbate	30 mg
d-calcium pantothenate	10 mg
Pyridoxine hydrochloride	5 mg
Cyanocobalamin	10 μg
Folic Acid (Folacin)	800 μg
D-Biotin	200 μg
Selenium (l-seleno-methionine)	100 μg
Chromium picolinate	50 μg
Zinc glycinate	15 mg
Calcium citrate	250 mg
Magnesium citrate	125 mg

Radioprotective Formulations: (boost formulations)

For Category 1 Personnel:

vitamin C (calcium ascorbate)	250 mg
natural source vitamin E (d-alpha tocopheryl acid succinate)	200 I.U.
N-acetyl cysteine	250 mg

Complete dosage to be taken 1 hour prior to an imaging study.

For Category 2 Personnel:

vitamin C (calcium ascorbate)	500 mg
natural source vitamin E (d-alpha tocopheryl acid succinate)	400 I.U.
N-acetyl cysteine	250 mg
beta-carotene (from natural *d. salina*)	15 mg
alpha lipoic acid	30 mg

Complete dosage to be taken 1 hour prior to an imaging study or prior to each flight.

For Category 3 Personnel:

vitamin C (calcium ascorbate)	500 mg
natural source vitamin E (d-alpha tocopheryl acid succinate)	400 I.U.
N-acetyl cysteine	250 mg
beta-carotene (from natural *d. salina*)	15 mg
alpha lipoic acid	30 mg

Complete dosage to be taken 1 hour prior to an imaging study and 24 hours and 48 hours after the imaging study.

For Category 4 Personnel:

vitamin C (calcium ascorbate)	500 mg
natural source vitamin E (d-alpha tocopheryl acid succinate)	400 I.U.
N-acetyl cysteine	250 mg
beta-carotene (from natural *d. salina*)	15 mg
alpha lipoic acid	30 mg

Complete dosage to be taken 24 hours and 1 hour prior to an imaging study and 24 hours after the imaging study.

For Category 5 Personnel:

vitamin C (calcium ascorbate)	500 mg
natural source vitamin E (d-alpha tocopheryl acid succinate)	400 I.U.
N-acetyl cysteine	500 mg
beta-carotene (from natural *d. salina*)	30 mg
alpha lipoic acid	60 mg

Complete dosage to be taken 48 hours, 24 hours, and 1 hour prior to an imaging study and 24 hours after the imaging study.

For Category 6 Personnel:

vitamin C (calcium ascorbate)	1000 mg
d-alpha tocopheryl acid succinate	400 I.U.
alpha tocopherol	200 I.U.
N-acetyl cysteine	500 mg
beta-carotene (from natural *d. salina*)	50 mg
alpha lipoic acid	100 mg

-continued

Complete dosage to be taken prior to anticipated exposure or as soon as possible after actual exposure. Continue complete dosage daily for seven days after exposure. For Category 7 Personnel:	
vitamin C (calcium ascorbate)	2000 mg
d-alpha tocopheryl acid succinate	600 I.U.
alpha tocopherol	200 I.U.
N-acetyl cysteine	1000 mg
beta-carotene (from natural *d. salina*)	100 mg
alpha lipoic acid	150 mg

Complete dosage to be taken prior to anticipated exposure or as soon as possible after actual exposure. Continue complete dosage daily for fourteen days after exposure.

It has been estimated that approximately 70-80% of the cellular damage induced by ionizing radiation is caused by free radicals (23). Therefore, it would be prudent to use agents that would quench these substances formed during x-ray exposure and protect the cells, organs, and total body from such injury.

Since World War II, extensive studies have been undertaken to identify radioprotective compounds that have been shown to be effective when administered before exposure to irradiation (2, 27). It is important to note that such compounds do not protect cells or organisms if they are administered after the ionizing radiation exposure. For modest radiation dose levels, the protective agents can be absorbed rapidly enough that they could be effective when given immediately before the exposure (within an hour or two). For higher levels of radiation dosage, it might be more desirable to achieve an established steady state of antioxidant concentration in the tissues initially, and then provide a booster dose of radioprotective agent immediately prior to exposure.

Research has determined that sulfhydryl (SH) compounds such as cysteamine, cystamine, and glutathione are among the most important and active intracellular antioxidants. Cysteamine protects animals against bone marrow (2, 31) and gastrointestinal (32) radiation syndromes. The rationale for the importance of SH compounds is further supported by observations in mitotic cells. These are the most sensitive to radiation injury in terms of cell reproductive death and are noted to have the lowest level of SH compounds. Conversely, S-phase cells, which are the most resistant to radiation injury using the same criteria, have demonstrated the highest levels of inherent SH compounds. In addition, when mitotic cells were treated with cysteamine, they became very resistant to radiation (33). It has also been noted that cysteamine may directly protect cells against induced mutations (2). Unfortunately, cysteamine is extremely toxic when administered to human beings and, therefore, cannot itself be utilized in a radioprotective antioxidant regimen.

Thus, other SH compounds sharing the same antioxidant characteristics must be considered. Glutathione is a very effective antioxidant. However, when ingested by human beings it is completely hydrolyzed in the intestine and, therefore, can not be used as a radioprotective agent. However, N-acetylcysteine (NAC) and alpha lipoic acid actively increase the intracellular levels of glutathione without causing any toxicity. These rapidly absorbed compounds are tolerated by humans very well and would provide protection against ionizing radiation damage when given prior to the exposure. Indeed, these agents have also been shown to be of radioprotective value in experimental systems (31-35). Additional antioxidants such as vitamin E (d-alpha tocopheryl succinate), vitamin C (as calcium ascorbate) and the carotenoids (particularly natural beta-carotene) have been shown to be of marked radioprotectant value in animals and in humans (2, 36-50). A very recent report by the Armed Forces Radiobiology Research Institute showed good protection by vitamin E against lethal doses of cobalt-60 in mice (51).

The natural beta-carotene was selected because it most effectively reduces radiation-induced transformation in mammalian cells in culture (47). The d-alpha tocopheryl succinate form of vitamin E was selected because it is the most effective form of this micronutrient (52) and also actively reduces the incidence of radiation-induced transformation in mammalian cells (53, 54). This form of vitamin E is a more effective antioxidant than the more commonly utilized alpha tocopherol or other mixtures of tocopherols (55). Vitamin C as calcium ascorbate is beneficial because it is the most effective nonacidic form available for human use and, therefore, is less likely to cause stomach upset, diarrhea, and other problems that are observed in some individuals when taking therapeutic doses of vitamin C.

The most effective antioxidant approach to the free radical damage related to ionizing radiation-induced injury must utilize multiple micronutrients. It has been determined that multiple antioxidants are more effective than the individual agents themselves, and we propose this approach for several reasons. It is known that vitamin C and vitamin E are synergistic as antioxidants against free radicals because they are able to protect both the aqueous and lipid environments of the cells respectively. Indeed, one study has shown that oral intake of both vitamin C and vitamin E reduces the levels of fecal mutagens formed during digestion more than that produced by either of the individual antioxidants (56). It also must be recognized that oxygen level may vary widely within the tissues of whole organs or within the individual cells. This is especially true during the biologic insults that may occur with radiation-induced damage. It is known that beta-carotene acts more effectively as an antioxidant in high oxygen pressures, whereas vitamin E is a more effective antioxidant at reduced oxygen pressures (57).

Finally, the body produces several types of free radicals (a myriad of oxygen-derived and nitrogen-derived species) during exposure to ionizing radiation. Clearly, each antioxidant has a different affinity for each specific class of free radicals. In a parallel manner, a combination of antioxidants is more effective in reducing the growth of tumor cells than the individual agents themselves (58). Therefore, to provide the most effective overall micronutrient approach to protect against radiation injury, a multiple component protocol utilized with a risk-based strategy seems essential and rational.

In the interest of clarity and conserving space, references in the foregoing have been given by number, parenthetically. These numbers relate to the following:

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What is claimed is:

1. A formulation consisting essentially of:

Vitamin A (palmitate)	5,000 I.U.
Beta-carotene (from natural D. salina)	15 mg
Vitamin D-3 (cholecalciferol)	400 I.U.
Natural soucre Vitamin E	
(d-alpha tocopherol)	100 I.U.
(d-alpha tocopheryl acid succinate)	100 I.U.
Buffered Vitamin C (calcium ascorbate)	500 mg
Thiamine mononitrate	4 mg
Riboflavin	5 mg
Niacinamide ascorbate	30 mg
d-calcium pantothenate	10 mg
Pyridoxine hydrochloride	5 mg
Cyanocobalamin	10 μg
Folic Acid (Folacin)	800 μg
D-Biotin	200 μg
Selenium (1-seleno-methionine)	100 μg
Chromium picolinate	50 μg
Zinc glycinate	15 mg
Calcium citrate	250 mg
Magnesium citrate	125 mg

and a booster formulation selected from a group consisting essentially of 1000 mg of vitamin C, 400 international units of d-alpha tocopheryl acid succinate, 200 international units of alpha tocopherol, 500 mg of N-acetyl cysteine, 50 mg of beta-carotene, and 100 mg of alpha lipoic acid, wherein said formulation is designed to reduce the risk in humans exposed to ionizing radiation of becoming subjected to at least one condition selected from the group consisting essentially of radiation-induced acute leukemia, breast cancer, and thyroid cancer.

2. The formulation of claim **1** wherein said dosage is taken prior to anticipated exposure.

3. The formulation of claim **1** wherein said dosage is taken after exposure.

4. The formulation of claim **1** wherein said formulation is taken by user after exposure for a period of at least seven days.

5. The formulation of claim **1** wherein said formulation is designed for a human who receives an effective dose of ionizing radiation of 0.5 mSv or less.

6. The formulation of claim **1** wherein said formulation is designed for a human who receives an effective dose of ionizing radiation of 0.5-5 mSv.

7. The formulation of claim **1** wherein said formulation is designed for a human who receives internal radionuclide exposures.

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