AUSTRALIA

GUIDANCE MANUAL

Medical Management of Individuals Involved in Radiation Accidents

PART 3 of 3

Appendix A6

TECHNICAL REPORT SERIES No. 131

AUSTRALIAN RADIATION PROTECTION AND NUCLEAR SAFETY AGENCY

ARPANSA

APPENDIX A6

The material in this Appendix is based on the REAC/TS *Guidance for Radiation Accident Management* and is reprinted with permission.

The original document is available from the REAC/TS WEB site at www.orau.gov/reacts

Guidance for Radiation Accident Management

Radiation Emergency Assistance Center/Training Site (REAC/TS)

Radiation Emergency Assistance Center/ Training Site (REAC/TS)

Oak Ridge Institute for Science and Education

CONTENTS

Managing Radiation Emergencies

Guidance for Prehospital **Emergency Services**

Managing Radiation Emergencies

Guidance for Hospital **Medical Management**

- Acute Radiation Syndrome
- Treatment of Internal Contamination
- Managing Emergency Care
  - Notification and Accident Verification
  - The Radiological Emergency Response Team
  - Goals of Contamination Control
  - Techniques of Contamination Control
  - If Radioactive Contamination Is Discovered After Patient Has Been Admitted
  - Response Team Preparation
  - Treatment Area Preparation
- Hospital Emergency Care of the Radiation Accident Patient
  - Patient Arrival and Triage
  - Assessment and Treatment of the Noncontaminated Patient
  - Assessment and Treatment of the Contaminated Patient
  - Radiological and Clinical Laboratory Assessments
  - Decontamination of the Contaminated Patient
  - Patient Comfort and Emotional Support
  - Patient Safety
  - Documentation
  - Post-Emergency Patient Transfer
  - Staff Exit from the Controlled Area

About REAC/TS

Radiation Emergency Assistance Center/Training Site (REAC/TS)

Since its formation in 1976, the Radiation Emergency Assistance Center/Training Site has provided support to the U.S. Department of Energy, the World Health Organization (WHO), and the International Atomic Energy Agency (IAEA) in the medical management of radiation accidents. A 24-hour emergency response program at the Oak Ridge Institute for Science and Education (ORISE), REAC/TS trains, consults, or assists in the response to all types of radiation accidents or incidents. The Center's specially trained team of physicians, nurses, health physicists, radiobiologists, and emergency coordinators is prepared around-the-clock to provide assistance on either the local, national, or international level.

Designated a WHO Collaborating Center in 1980, REAC/TS is recognized around the world for its expertise and is called upon to assist the global community in providing medical care to radiation accident victims, either directly or indirectly as consultants. REAC/TS staff bring this valuable experience to the classroom in their delivery of several different training courses that address the medical aspects of radiation accident management. Taught both at the unique REAC/TS facility in Oak Ridge, Tenn., and at the various hospitals and nuclear facilities across the country, these courses train physicians, physicians' assistants, nurses, health physicists, and others who may have to respond to a radiation accident. Through lectures, discussions, and exercises, these participants learn the roles they play in the medical management of a radiation accident.

For more information on REAC/TS, e-mail cooleyp@orau.gov or write:

Oak Ridge Institute for Science and Education
REAC/TS
Attn: Pat Cooley
P.O. Box 117, MS 39
Oak Ridge, TN 37831-0117
Phone: +1 865 576 3131
FAX: +1 865 576 9522

BASICS OF RADIATION

Radiation is energy that comes from a source and travels through some material or through space. Light, heat and sound are types of radiation. The kind of radiation discussed in this presentation is called ionizing radiation because it can produce charged particles (ions) in matter.

Ionizing radiation is produced by unstable atoms. Unstable atoms differ from stable atoms because they have an excess of energy or mass or both.

Unstable atoms are said to be radioactive. In order to reach stability, these atoms give off, or emit, the excess energy or mass. These emissions are called radiation. The kinds of radiation are electromagnetic (like light) and particulate (i.e., mass given off with the energy of motion). Gamma radiation and X-rays are examples of electromagnetic radiation. Beta and alpha radiation are examples of particulate radiation. Ionizing radiation can also be produced by devices such as X-ray machines.

There is also natural background radiation exposure. It comes from cosmic rays and from naturally occurring radioactive materials contained in the earth and in living things.

Irradiation

Irradiation is exposure to penetrating radiation. Irradiation occurs when all or part of the body is exposed to radiation from an unshielded source. *External irradiation does not make a person radioactive.*

Radioactive Contamination

Contamination occurs when material that contains radioactive atoms is deposited on skin, clothing, or any place where is it not desired. If is important to remember that radiation does not spread or get "on" or "in" people; rather it is radioactive contamination that can spread. A person contaminated with radioactive materials will be irradiated until the source of radiation (the radioactive material) is removed.

- A person is *externally* contaminated if radioactive material is on skin or clothing.
- A person is *internally* contaminated if radioactive material is breathed in, swallowed, or absorbed through wounds.
- The *environment* is contaminated if radioactive material is spread about or uncontained.

Characteristics of Gamma Radiation and X-Rays

1. Gamma radiation and X-rays are electromagnetic radiation like visible light, radio waves, and ultraviolet light. These electromagnetic radiations differ only in the amount of energy they have. Gamma rays and X-rays are the most energetic of these.

2. Gamma radiation is able to travel many meters in air and many centimeters in human tissue. It readily penetrates most materials and is sometimes called "penetrating radiation."

3. X-rays are like gamma rays. They, too, are penetrating radiation.

4. Radioactive materials that emit gamma radiation and X-rays constitute both an external and internal hazard to humans.

5. Dense materials are needed for shielding from gamma radiation. Clothing and turnout gear provide little shielding from penetrating radiation but will prevent contamination of the skin by radioactive materials.

6. Gamma radiation is detected with survey instruments, including civil defense instruments. Low levels can be measured with a standard Geiger counte. High levels can be measured with an ionization chamber.

7. Gamma radiation or X-rays frequently accompany the emission of alpha and beta radiation.

8. Instruments designed solely for alpha detection (such as an alpha scintillation counter) will not detect gamma radiation.

9. Pocket chamber (pencil) dosimeters, film badges, thermoluminescent, and other types of dosimeters can be used to measure accumulated exposure to gamma radiation.

Characteristics of Beta Radiation

1. Beta radiation may travel meters in air and is moderately penetrating.

2. Beta radiation can penetrate human skin to the "germinal layer," where new skin cells are produced. If beta-emitting contaminants are allowed to remain on the skin for a prolonged period of time, they may cause skin injury.

3. Beta-emitting contaminants may be harmful if deposited internally.

4. Most beta emitters can be detected with a survey instrument (provided the metal probe cover is open). Some beta emitters, however, produce very low energy, poorly penetrating radiation that may be difficult or impossible to detect. Examples of these are carbon-14, tritium, and sulfur-35.

5. Beta radiation cannot be detected with an ionization chamber

6. Clothing and turnout gear provide some protection against most beta radiation. Turnout gear and dry clothing can keep beta emitters off of the skin.

Characteristics of Alpha Radiation

1. Alpha radiation is not able to penetrate skin.

2. Alpha-emitting materials can be harmful to humans if the materials are inhaled, swallowed, or absorbed through open wounds.

3. A variety of instruments have been designed to measure alpha radiation. Special training in use of these instruments is essential for making accurate measurements.

4. A civil defense instrument cannot detect the presence of radioactive materials that produce alpha radiation unless the radioactive materials also produce beta and/or gamma radiation.

5. Instruments cannot detect alpha radiation through even a thin layer of water, blood, dust, paper, or other material, because alpha radiation is not penetrating.

6. Alpha radiation travels a very short distance through air.

7. Alpha radiation is not able to penetrate turnout gear, clothing, or a cover on a probe. Turnout gear and dry clothing can keep alpha emitters off of the skin.

Definitions

Alpha particle: A specific particle ejected from a radioactive atom. It has low penetrating power and short range. Alpha particles will generally fail to penetrate the skin. Alpha-emitting atoms can cause health effects if introduced into the lungs or wounds.

Atom: The smallest piece of an element that cannot be divided or broken up by chemical means.

Background radiation: The radiation in man's natural environment, including cosmic rays and radiation from the naturally radioactive elements, both outside and inside the bodies of humans and animals. It is also called natural radiation. Man-made sources of radioactivity contribute to total background radiation levels.

Becquerel: The SI unit of activity 1 disintegration per second; 37 billion Bq = 1 curie. (See conversion factors in the Measurement section.)

Beta particle: A small particle ejected from a radioactive atom. It has a moderate penetrating power and a range of up to a few meters in air. Beta particles will penetrate only a fraction of an inch of skin tissue.

Controlled area: An area where entry, activities, and exit are controlled to help ensure radiation protection and prevent the spread of contamination.

Cosmic rays: High-energy radiation that originates outside the Earth's atmosphere.

Contamination: Deposition of radioactive material in any place where it is not desired, particularly where its presence can be harmful.

Curie: A unit of measure used to describe the amount of radioactivity in a sample of material.

Decontamination: The reduction or removal of contaminating radioactive material from a structure, area, object, or person.

Detector: A device that is sensitive to radiation and can produce a response signal suitable or measurement or analysis. A radiation detection instrument.

Dose: A general term for the quantity of radiation or energy absorbed.

Dose rate: The dose delivered per unit of time. It is usually expressed as rads per hour or in multiples or submultiples of this unit such as millirads per hour. The dose rate is commonly used to indicate the level of hazard from a radioactive source.

Dosimeter: A small, pocket-sized device used for monitoring radiation exposure of personnel. Before use, it is given a charge, and the amount of discharge that occurs is a measure of the accumulated radiation exposure.

Electromagnetic radiation: A traveling wave motion that results from changing electric and magnetic fields. Types of electromagnetic radiation range from those of short wavelength, like x rays and gamma rays, through the ultraviolet, visible, and infrared regions, to radar and radio waves of relatively long wavelengths.

Exposure: A quantity used to indicate the amount of ionization in air produced by x- or gamma-ray radiation. The unit is the roentgen (R). For practical purposes, one roentgen is comparable to 1 rad or 1 rem for X and gamma radiation. The SI unit of exposure is the coulomb per kilogram (C/kg). One R = 2.58×10^{-4} C/kg.

Gamma rays, or gamma radiation: Electromagnetic radiation of high energy. Gamma rays are the most penetrating type of radiation and represent the major external hazard.

Geiger counter or G-M meter: An instrument used to detect and measure radiation.

Gray: The SI unit of absorbed dose; 1 gray = 100 rads.

Inverse square law: The relationship that states that electromagnetic radiation intensity is inversely proportional to the square of the distance from a point source.

Ionization: Production of charged particles in a medium. An orbital electron is stripped from a neutral atom, producing an ion pair (a negatively charged electron and a positively charged atom).

Ionizing radiation: Electromagnetic (X ray and gamma) or particulate (alpha, beta) radiation capable of producing ions or charged particles.

Irradiation: Exposure to ionizing radiation.

Monitoring: Determining the amount of ionizing radiation or radioactive contamination present. Also referred to as surveying.

Rad: The unit of radiation absorbed dose.

Radiation: Energy traveling through space. Some types of radiation associated with radioactivity are alpha and beta particles and gamma and X rays.

Radioactivity: The spontaneous emission of radiation from the nucleus of an unstable atom. As a result of this emission, the radioactive atom is converted, or decays, into an atom of a different element that might or might not be radioactive.

Rem: A measure of radiation dose related to biological effect.

Roentgen: The unit of exposure from X or gamma rays (see exposure).

Sealed source: A radioactive source, sealed in an impervious container that has sufficient mechanical strength to prevent contact with and dispersion of the radioactive material under the conditions of use and wear for which it was designed. Generally used for radiography or radiation therapy. May be classified "Special Form" on shipping papers and packages.

Sievert: The SI unit of dose equivalent; 1 Sv = 100 rem.

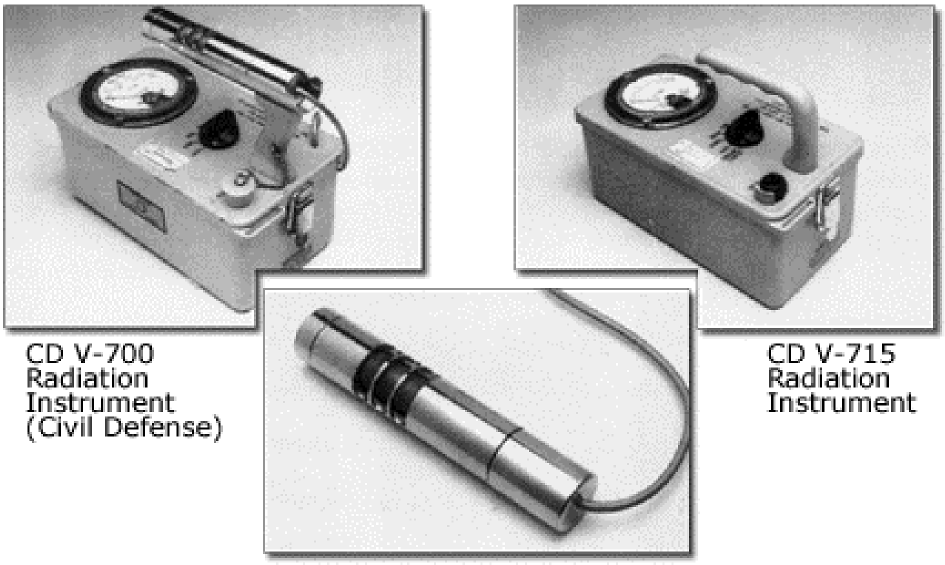
X rays: Penetrating electromagnetic radiation whose wavelengths are shorter than those of visible light.

DETECTION

How to Detect Radiation

Radiation cannot be detected by human senses. A variety of instruments are available for detecting and measuring radiation.

Examples of radiation survey meters:



CD V-700 Radiation Instrument (Civil Defense)

CD V-715 Radiation Instrument

Close-up view of probe from CD V-700 with window open

Using a Geiger-Mueller (GM) Counter to Survey

Get the GM counter and batteries from storage; prepare the instrument and determine background level.

Preparing the Meter:

- Position the Geiger counter with the meter away from you. Locate and open the battery compartment.
- Put the batteries in the meter using proper orientation (up/down).
- Close and latch the battery compartment.
- Check the batteries using the "range" switch or "bat" button; the method depends on the type of instrument. The meter needle should move to area on scale marked battery, indicating the batteries are good. If the batteries are not good, find a flashlight or other source of 2 D-cells and put them in the meter -- check these batteries also.
- Turn the "F/S" switch to "S" (Slow).
- Turn the "audio" switch to "ON."

Measuring the Background Radiation:

- Check that the "F/S" switch is on "S" (Slow).
- Move the range switch to the most sensitive position.
- Remove the probe cover if one is in place.
- Measure the background radiation for 60 seconds: write down the reading. Since background radiation varies with time, it may be desirable to make several counts and average the results. Record the reading.
- Expect a reading of 40-100 counts/min or a reading of approximately 0.2 μSv/hr. (i.e. 0.2 on the 0.1 range setting),
- Record background reading.

How to Survey

Using the instrument:

- Move the "F/S" switch to "F" (Fast response).
- Set the instrument selector switch to the most sensitive range of the instrument.
- Holding the probe approximately 1/2 to 1 inch from the person's skin, systematically survey the entire body from head to toe on all sides.
  - Move the probe slowly (about 1 inch per second).
  - Do not let the probe touch anything.
  - Try to maintain a constant distance.
  - Pay particular attention to hands, face and feet.
  - Note that some GM instruments cannot detect alpha radiation and some low-energy beta radiation. Because alpha radiation is non-penetrating, it cannot be detected through even a thin film of water, blood, dirt, clothing, or through probe cover.

An increase in count rate or exposure rate above background indicates the presence of radiation.

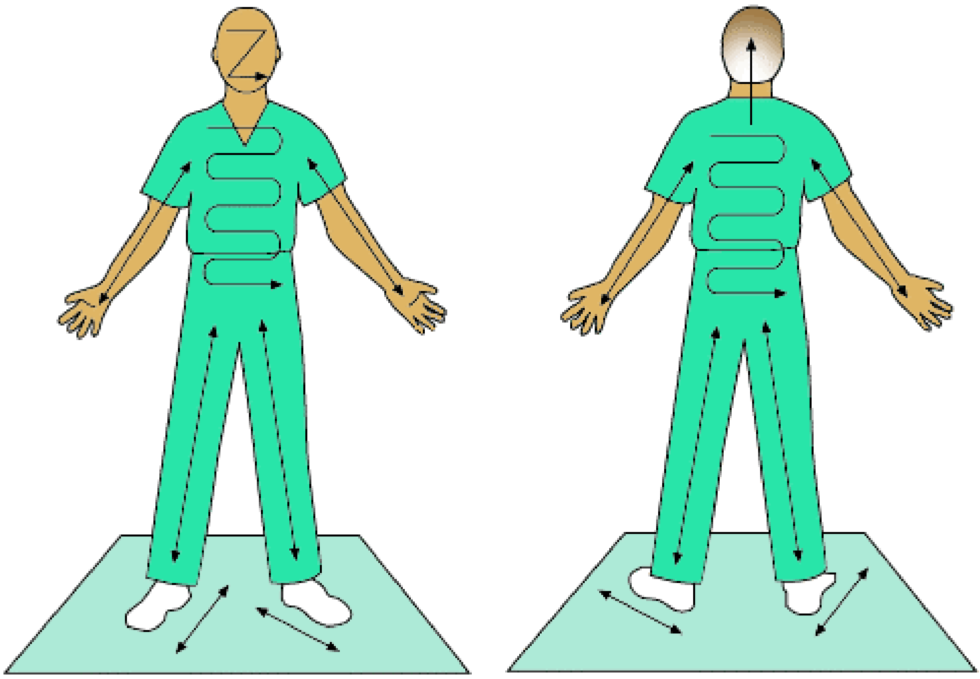
- Locate the point that produces the most clicks. (Turn the "F/S" switch to "S" to take a reading at this location. Remember to reset it to "F" before continuing survey.)
- When necessary, adjust the range of the instrument by moving the range selector switch.
- Document time and radiation measurements.
- In general, areas that register more than twice the previously determined background level are considered contaminated. For accidents involving alpha emitters, if the reading is less

than twice the background radiation level, the person is not contaminated to a medically significant degree. If the accident circumstances indicate that an alpha emitter (such as plutonium) or low energy beta emitter could be a contaminant, a health physicist should always be consulted.

Ending the radiation survey:

- Switch off the meter.
- Replace the cap on the meter probe.
- Take the batteries out.
- Put the Geiger counter back in its case.

Personnel monitoring



1. Have the person stand on a clean pad.
2. Instruct the person to stand straight, feet spread slightly, arms extended with palms up and fingers straight out.
3. Monitor both hands and arms; then repeat with hands and arms turned over.
4. Starting at the top of the head, cover the entire body, monitoring carefully the forehead, nose, mouth, neckline, torso, knees, and ankles.
5. Have the subject turn around, and repeat the survey on the back of the body.
6. Monitor the soles of the feet.

MEASUREMENT

Activity: How Much Is Present?

The size or weight of a container or shipment does not indicate how much radioactivity is in it.

The amount of radioactivity in a quantity of material can be determined by noting how many curies of the material are present. This information should be found on labels and/or shipping papers.

More curies = a greater amount of radioactivity

A large amount of material can have a very small amount of radioactivity; a very small amount of material can have a lot of radioactivity.

For example, uranium-238 has 0.00015 curies of radioactivity per pound (0.15 millicuries), while cobalt-60 has nearly 518,000 curies per pound.

In the International System of units (SI), the becquerel (Bq) is the unit of radioactivity. One Bq is 1 disintegration per second (dps). One curie is 37 billion Bq. Since the Bq represents such a small amount, you are likely to see a prefix used with Bq, as shown below:

- 1 MBq (27 microcuries)
- 1 GBq (27 millicuries)
- 37 GBq (1 curie)
- 1 TBq (27 curies)

SI Units and Prefixes

The International System of Units has been given official status and recommended for universal use by the General Conference on Weights and Measures.

Radiation Measurements

	Radioactivity	Absorbed Dose	Dose Equivalent	Exposure
Common Units	curie (Ci)	rad	rem	roentgen (R)
SI Units	becquerel (Bq)	gray (Gy)	sievert (Sv)	coulomb/kilogram (C/kg)

Following is a list of prefixes and their meanings that are often used in conjunction with SI units:

Multiple	Prefix	Symbol
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10^{-2}	centi	c
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n

Conversions

Conversion Equivalence

1 curie = 3.7 x 10^{10} disintegrations per second		1 becquerel = 1 disintegration per second
1 millicurie (mCi)	=	37 megabecquerels (MBq)
1 rad	=	0.01 gray (Gy)
1 rem	=	0.01 sievert (Sv)
1 roentgen (R)	=	0.000258 coulomb/kilogram (C/kg)
1 megabecquerel (MBq)	=	0.027 millicuries (mCi)
1 gray (Gy)	=	100 rad
1 sievert (Sv)	=	100 rem
1 coulomb/kilogram (C/kg)	=	3,880 roentgens

Conversion Factors

To convert from	To	Multiply by
Curies (Ci)	becquerels (Bq)	3.7×10^{10}
millicuries (mCi)	megabecquerels (MBq)	37
microcuries (µCi)	megabecquerels (MBq)	0.037
millirads (mrad)	milligrays (mGy)	0.01
millirems (mrem)	microsieverts (µSv)	10
milliroentgens (mR)	microcoulombs/kilogram (µC/kg)	0.258
becquerels (Bq)	curies (Ci)	2.7×10^{-11}
megabecquerels (MBq)	millicuries (mCi)	0.027
megabecquerels (MBq)	microcuries (µCi)	27
milligrays (mGy)	millirads (mrad)	100
microsieverts (µSv)	millrems (mrem)	0.1
microcoulombs/kilogram (µC/kg)	milliroentgens (mR)	3.88

SAFETY AROUND RADIATION SOURCES

Too much radiation exposure is harmful. The degree of radiation injury depends on the amount of radiation received and the time involved. In general, the higher the amount, the greater the severity of early effects (occurring within a few weeks) and the greater the possibility of late effects such as cancer.

The **BEIR V** (Biological Effects of Ionizing Radiation**)** Committee of the National Research Council estimates that among 100,000 people exposed to a one-time dose of 10 rem (10,000 mrem) and followed over their life span, about 790 more would die of cancer than the estimated 20,000 cancer deaths that would be expected among a non-exposed group of the same size. NOTE: 10 rem = 100 millisieverts (100 mSv).

Radiation from Various Sources

- Natural cosmic and terrestrial radiation: U.S. average: 600 microSv/yr (60 mrem)
- Natural radioactivity in body tissue: 400 microSv/yr (40 mrem)
- Air travel round trip (London-New York): 40 microSv each way (4 mrem)
- Chest X-ray: 100 microSv per test (10 mrem)
- Radon in the home: 2 milliSv/yr (200 mrem) variable
- Man-made (medicine, other): 600 microSv/yr (60 mrem)

Keeping Exposure Low

Although some radiation exposure is natural in our environment, it is desirable to limit radiation exposure as much as is possible or practical.

Radiation Protection Guidelines

Time: The shorter the time in a radiation field, the less the radiation exposure. Work quickly and efficiently. A rotating team approach can be used to keep individual radiation exposures to a minimum.

Distance: The farther a person is from a source of radiation, the lower the radiation dose. Do not touch radioactive materials. Use shovels, brooms, etc., to move materials to avoid physical contact.

Shielding: Although not always practical in emergency situations, shielding offered by barriers can reduce radiation exposure.

Quantity: Limit the amount of radioactive material in the working area to decrease exposure.

Emergency responders have never received exposures of medical concern in any radiation accident in the United States.

WORKING SAFELY AROUND RADIOACTIVE CONTAMINATION

Emergency Services

1. Avoid contact with contaminants.

2. Wear protective clothing (such as fire turnout gear, coveralls, gloves, and boots) that, if contaminated, can be removed.

3. Use full respiratory protection if fire, smoke, fumes, gases, or windblown dusts are present.

4. As soon as possible after proper care of the victim and resolution of the emergency situation, wash any part of you that may have come in contact with contamination.

5. Assume that all materials, equipment and personnel have been contaminated if they were in the immediate area of the incident. Radiological monitoring is recommended before leaving the scene.

6. Do not eat, drink, smoke, rub eyes, or apply makeup within contaminated areas.

7. If in doubt, assume contamination.

Like dirt, most contamination washes off with soap and water.

Hospital

General:

1. If in doubt, assume contamination.

2. Avoid contact with contaminants.

3. Do not eat, drink, or smoke in areas where radioactive materials are located.

When providing emergency care:

1. Set up a controlled area large enough to hold the anticipated number of victims
2. Prevent tracking of contaminants by covering floor areas and monitoring exits of controlled areas.
3. Restrict access to the controlled area.
4. Monitor *anyone* or *anything* leaving the controlled area.
5. Use strict isolation precautions, including double bagging and protective clothing. (Protective clothing such as gowns, caps, masks, boots, gloves, that, if contaminated, can be removed.)
6. Use a buffer zone or secondary control line for added security.
7. Control waste by using large, plastic-lined containers for clothing, linens, dressings, etc.
8. Control ventilation.
9. Change instruments, outer gloves, drapes, etc., when they become contaminated.
10. Use waterproof materials to limit the spread of contaminated liquids, for example, waterproof aperture drapes.

TYPES OF RADIATION EXPOSURE

Regardless of where or how an accident involving radiation happens, three types of radiation-induced injury can occur: external irradiation, contamination with radioactive materials, and incorporation of radioactive material into body cells, tissues, or organs.

External Irradiation

External irradiation occurs when all or part of the body is exposed to penetrating radiation from an external source. During exposure this radiation can be absorbed by the body or it can pass completely through. A similar thing occurs during an ordinary chest x-ray. Following external exposure, an individual is not radioactive and can be treated like any other patient. (Refer to the sections on assessment and treatment in *Hospital Emergency Care of the Radiation Accident Patient.)*

Contamination

The second type of radiation injury involves *contamination* with radioactive materials. Contamination means that radioactive materials in the form of gases, liquids, or solids are released into the environment and contaminate people externally, internally, or both. An external surface of the body, such as the skin, can become contaminated, and if radioactive materials get inside the body through the lungs, gut, or wounds, the contaminant can become deposited internally. Refer *to Managing Emergencies Involving Radiation* for additional information.

Incorporation

The third type of radiation injury that can occur is *incorporation* of radioactive material. Incorporation refers to the uptake of radioactive materials by body cells, tissues, and target organs such as bone, liver, thyroid, or kidney. In general, radioactive materials are distributed throughout the body based upon their chemical properties. Incorporation cannot occur unless contamination has occurred. (Refer to the section on assessment and treatment of the contaminated patient in *Hospital Emergency Care of the Radiation Accident Patient.*)

These three types of exposures can happen in combination and can be complicated by physical injury or illness. In such a case, serious medical problems always have priority over concerns about radiation, such as radiation monitoring, contamination control, and decontamination.

Biological Effects of Acute, Total Body Irradiation	
Amount of Exposure	**Effect**
• 50 mGy (5 rads)	No detectable injury or symptoms
• 1 Gy (100 rads)	May cause nausea and vomiting for 1-2 days and temporary drop in production of new blood cells
• 3.5 Gy (350 rads)	Nausea and vomiting initially, followed by a period of apparent wellness. At 3-4 weeks, there is a potential for deficiency of white blood cells and platelets. Medical care is required.
• Higher levels of exposure can be fatal. Medical care is required.	

GUIDANCE FOR PRE-HOSPITAL EMERGENCY SERVICES

Introduction

Radioactive materials are among the many kinds of hazardous substances emergency responders might have to deal with in a transportation accident. Because strict packaging requirements are used in the shipment of radioactive materials, accidental spills or releases of these substances seldom occur. Very few emergency responders have ever had to deal with transportation accidents involving radioactive materials, and these accidents will continue to be rare occurrences. Nevertheless, it is prudent for you, as an emergency responder, to know your role in responding to such an accident should one occur in your community.

Like most emergency first responders, you might have questions about these accidents and your involvement in them. This information was written to answer questions most frequently asked by firefighters, law enforcement officers, and medical emergency medical services personnel. Remember that some radioactive materials can also be chemically hazardous. Use the appropriate guide during any transportation accident involving hazardous material.

Guidelines for Incident Command

1. Approach site with caution. Position personnel, vehicles, and command post at a safe distance upwind and uphill of the site, if possible.

2. Ensure safety of responders.

   - Identify all hazards (danger of fire, explosion, toxic fumes, electrical hazards, structural collapse, etc.).
   - Identify cargo.
   - Obtain information concerning the cargo from placards, labels, shipping documents, and other immediately available sources.
   - Keep upwind of smoke, fumes, etc.
   - Follow usual protocols for respiratory protection, use of protective clothing, and turnout gear.
   - Monitor changing conditions that could create hazardous situations.

3. Locate victims and facilitate extrication, emergency care and transportation of the injured. **Medical problems take priority over radiological concerns. Do not delay rescue or transport of a seriously injured, contaminated patient.**

4. Communications

   - Notify hospital of possible contamination/exposure of victim.
   - Notify state radiological assistance (emergency response center) of accident conditions.

5. Establish a control zone

   - Reroute traffic.
   - Mark controlled area by use of ropes or tapes.
   - Limit entry to rescue personnel only.
   - Order evacuation or sheltering as needed.

6. Prevent/fight fires as if toxic chemicals are involved.

7. Ensure radiation protection and contamination control.

- Do not allow eating, drinking, smoking, or other activities within contaminated areas that might lead to intake of radioactive material.

- Avoid direct contact with radioactive materials where possible. Utilize protective clothing and anything available for remote handling (shovels, branches, ropes, etc.)

- Limit time near radioactive materials to the minimum necessary. Rotate staff as necessary.

- Determine radiation levels within controlled area and monitor rescue personnel with individual dosimeters, if available.

- Evacuate personnel from the immediate downwind area. Detain personnel who were in the accident area until they can be checked by radiological monitors. Follow instruction of radiation authority.

- Remove protective gear/clothing at the control line.

- Wrap, label, and isolate all clothing, tools, etc. used in the controlled area, and retain them until they can be cleared by radiation authority.

- Determine if measures are needed to contain all accident debris in the control zone until cleanup is achieved. Prevent unnecessary handling of incident debris.

8. Documentation

- Record the names and addresses of all persons involved, including those who insist on leaving the area; rescuers; those removed for medical attention; and ambulance personnel.

- Make detailed records of the incident.

9. Remain calm.

- Do not be overly concerned with the presence of radioactive material or allow it to disrupt usual emergency response

- activities. Remember, it is improbable that emergency personnel will receive any radiation injury during these operations.

10. Delay cleanup pending instruction from radiation authority. Coordinate cleanup activities at site with public officials.

- Response actions may be performed before any radiation measurements. Some radioactive materials cannot be detected by commonly available instruments.

Hazard Identification

What do the labels for packages of radioactive materials indicate?

All shipments of radioactive material, with the exception of those containing limited quantities or those of low specific activity (LSA), bear two identifying warning labels affixed to opposite sides of the outer package. Three different labels -- White-I, Yellow-II, or Yellow-III -- are used on the external surface of packages containing radioactive material.

The U.N. hazard class "7" is on labels of radioactive material.

Package labels specify the radioactive content and the quantity in curies. Yellow-II and Yellow-III also specify the transport index.

Label	Radiation Level Associated With Intact Package	Symbol
Radioactive White-I	Almost no radiation--0.5 mrem/hr (5 μSv/hr) maximum on surface	
Radioactive Yellow-II	Low radiation levels--50 mrem/hr (0.5 mSv/hr) maximum on surface; 1 mrem/hr (10 μSv/hr) maximum at 1 meter	
Radioactive Yellow-III	Higher radiation levels--200mrem/hr (2 mSv/hr) maximum on surface;[a] 10 mrem/hr (0.1 mSv/hr) maximum at 1 meter Also required for fissile class III or large-quantity shipments, regardless of radiation level	

[a] "Exclusive use" shipments may be up to 0.01 Sv/hr (1 rem/hr), provided an enclosed vehicle is used. An unenclosed shipment (e.g., on a flatbed truck) may not exceed 2 μSv/hr (200 mrem/hr) on the surface.

What do the placards for shipment of radioactive material indicate?

Typical radioactive material warning placard

Standard size is 10 x 10 inches.

The placard shown must be used anytime a vehicle carries one or more packages of a Radioactive Yellow III label or if the vehicle is operating under exclusive use provisions required for certain LSA shipments or packages with higher than normal radiation levels.

Any four-digit ID number shown on an adjacent **orange panel** is used for specific identification of the cargo. The panel to the left bears the international identification number (International Series) for radioactive material, LSA, n.o.s. (material containing uniformly distributed radioactive material in low concentrations). This is the same four-digit ID number that must appear with the proper shipping name on the package as well as on the shipping documents.

The number "7" at the bottom of the placard is the U.N. hazard class description for radioactive materials.

Most shipments of radioactive material are accompanied by documents, such as shipping papers or bills of lading, which are of great value in assessing potential hazards in transportation accidents. These papers will have a 24-hour contact number for information about the material and potential health hazards.

Limits for Non-Exclusive Use Vehicle

2 mSv/hr (200 mrem/hr) at surface of package

Individual packages cannot exceed 0.1 mSv/hr (10 mrem/hr) at 1 meter

Limits for Exclusive Use Vehicle

20 µSv/hr (2 mrem/hr) in cab

2 mSv/hr (200 mrem/hr) on surface of vehicle

0.1 mSv/hr (10 mrem/hr) maximum at 2 meters

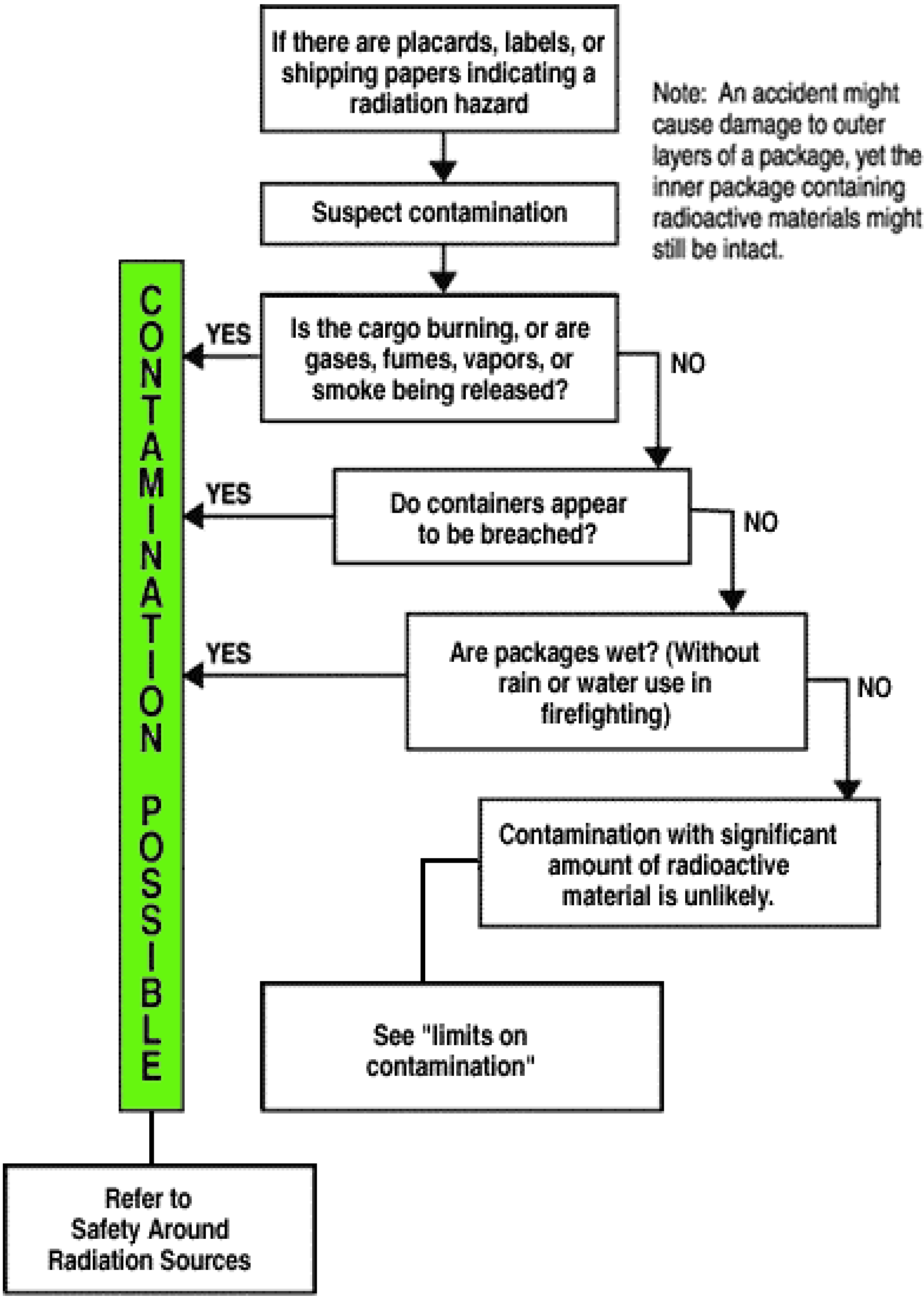
What is the transport index?

The number given indicates the maximum radiation level (in mrem/hr) at a distance of one meter from the external surface of a package or container.

(Readings in mSv/hr are multiplied by 100 to get mrem/hr.) For example, a TI of 3 (as shown above) would indicate that, at one meter from the labeled package, the radiation intensity that can be measured is no more than 3 mrem/hr (.03 mSv/hr).

If the radiation level at one meter from a package is found to be higher than the specified value, a radiation authority should be consulted. The package contents might have shifted, shielding might have been breached, or an error might have occurred in packaging or labeling.

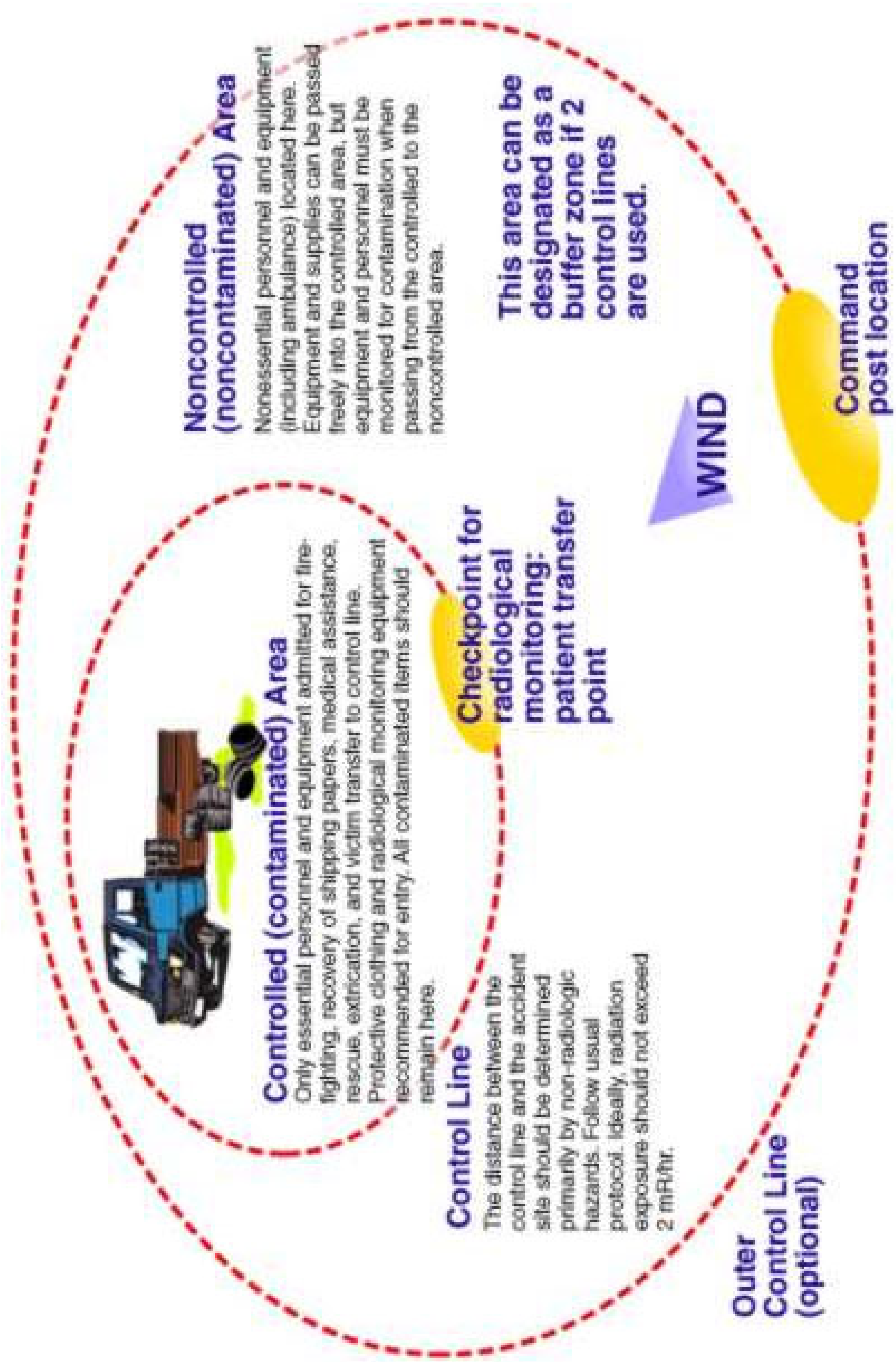
Is contamination possible?



A Comparison of Transportation Accidents Based on Type of Contaminant

	Toxic/Hazardous Chemicals	Radioactive Material
Is the material immediately threatening to the lives of rescuers and victims?	Possibly	Very unlikely
Is respiratory protection (SCBA) recommended for emergency response?	Yes	* Yes, if fire, fumes, smoke, or chemicals are involved or if environmental conditions could cause material to be airborne.
Is special protective clothing recommended for emergency response?	Yes	* Protective clothing, turnout gear, or other clothing that covers bare skin can keep contaminants off skin.
Does contamination with material produce visible early skin injury (i.e., redness, blistering, or rash that is not due to heat or flames)?	Possibly, if corrosive or toxic.	No. If these symptoms occur, look for other causes.
Does exposure cause immediate symptoms such as coughing, choking, burning eyes, vomiting, pain, etc., or unconsciousness?	Possibly	No. If these symptoms occur, look for other causes.
Are instruments for detection and measurement of hazard readily available?	No	Yes
Can human exposure be measured at the accident scene?	No	Yes

Establishing a Control Zone



Guidelines for Emergency Medical Management

1. Approach site with caution--look for evidence of hazardous materials.

2. If radiation hazard is suspected, position personnel, vehicles, and command post at a safe distance (approx. 150 feet) upwind and uphill of the site.

3. Notify proper authorities and hospital.

4. Put on protective gear and use dosimeters and survey meters if immediately available.

5. Determine whether injured victims are present.

6. Assess and treat life-threatening injuries immediately. Do not delay advanced life support if victims cannot be moved or to assess contamination status. Perform routine emergency care during extrication procedures.

7. Move victims away from the radiation hazard area, using proper patient transfer techniques to prevent further injury. Stay within the controlled zone if contamination is suspected.

8. Expose wounds and cover with sterile dressings.

9. Victims should be monitored at the control line for possible contamination only after they are medically stable. Radiation levels above background indicate the presence of contamination. Remove the contaminated accident victims' clothing, provided removal can be accomplished without causing further injury.

10. Move the ambulance cot to the clean side of the control line and unfold a clean sheet or blanket over it. Place the victim on the covered cot and package for transport. Do not remove the victim from the backboard if one was used.

11. Package the victim by folding the stretcher sheet or blanket over and securing them in the appropriate manner.

12. Before leaving the controlled area, rescuers should remove protective gear at the control line. If possible, the victim should be transported by personnel who have not entered the controlled area. Ambulance personnel attending victims should wear gloves.

13. Transport the victims to the hospital emergency department. The hospital should be given additional appropriate information, and the ambulance crew should ask for any special instructions the hospital may have.

14. Follow the hospital's radiological protocol upon arrival.

15. The ambulance and crew should not return to regular service until the crew, vehicle, and equipment have undergone monitoring and necessary decontamination by the radiation safety officer.

16. Personnel should not eat drink, smoke, etc., at the accident site, in the ambulance, or at the hospital until they have been released by the radiation safety officer.

Reference: Ricks, R.C., Prehospital/ Management of Radiation Accidents, ORAU 223, Oak Ridge Associated Universities, Oak Ridge, TN, 1984.

General Guidelines for Responding to a Fire

- Some materials may react with water or water vapor in air to form a hazardous vapor.
- Small Fires: Dry chemical, CO_2, Halon, water spray, or regular foam.
  Large Fires: Water spray, fog, or regular foam.
- Move undamaged containers from fire area if you can do it without risk. Do not touch damaged containers.
- Cool containers that are exposed to flames with water from the side until well after fire is out.
- Fight fire as if toxic chemicals are involved. To the extent possible, keep upwind and avoid smoke, fumes, gases, and dusts.
- For massive fire in cargo area, use unmanned hose holder or monitor nozzles; if this is impossible, withdraw from area and let fire burn.
- Stay away from ends of tanks. Withdraw immediately in case of rising sound from a venting safety device or if there is discoloration of tanks due to fire. Fight fires from maximum distance.
- Delay cleanup until radiation authority provides guidance.
- As much as possible, form barrier to contain fire, water that may be contaminated with radioactive, and/or other chemicals.

Use established fire-fighting procedures and protocols. Radioactivity does not change flammability or other properties of materials.

General Guidelines for Responding to a Spill or Leak

- Shut off ignition sources; no flares, smoking, or flames in hazard area.
- Keep combustibles (wood, paper, oil, etc.) away from spilled material.
- Do not touch spilled material. Do not touch damaged containers or move anything, except to rescue people.
- Detour pedestrian and vehicular traffic.
- Detain anyone who has been in the area of the spill or area of suspected contamination (except for victims requiring emergency medical care).
- Delay cleanup until the authorities arrive.
- Minimize dispersal of material (by wind, rain, etc.) by covering with a tarp, plastic sheet, etc. Tie down or use weights as necessary.
- If a right-of-way must be cleared before radiological emergency assistance arrives, move vehicles and debris the shortest distance required to open a pathway. Then, before permitting traffic to pass on the cleared path, spillage should be washed or wetted and swept to the edge with a minimum dispersal of wash water and spilled material.
- If radiation protection experts are not able to get to the scene within a reasonable period of time because of weather or other constraints and prompt action is required, do the following:

  Small Spills: Cover with sand or other noncombustible absorbent material and place into containers for later disposal.

  Large Spills: Build a dike far ahead of the spill to contain spilled material for later disposal.

  Note: Some radioactive materials may be corrosive.

GUIDANCE FOR HOSPITAL MEDICAL MANAGEMENT

Radiation Injury

Exposure to high levels of penetrating radiation can involve the whole body (uniformly or nonuniformly), a significant portion of the body, or a small, localized part. The exposure can be acute, protracted, or fractionated over time.

Local Injury

Most radiation injuries are "local" injuries, frequently involving the hands. These local injuries seldom cause the classical signs and symptoms of the acute radiation syndrome.

Consider local radiation injury in the differential diagnosis if the patient presents with a skin lesion without a history of chemical or thermal burn, insect bite, or history of skin disease or allergy. If the patient gives a history of possible radiation exposure (such as from a radiography source, X-ray device, or accelerator) or a history of finding and handling an unknown metallic object, note the presence of any of the following: erythema, blistering, dry or wet desquamation, epilation, ulceration. Local injuries to the skin evolve very slowly over time and symptoms may not manifest for days to weeks after exposure.

Conventional wound management is usually ineffective in these cases. **Consultation with experts regarding definitive diagnosis, tissue dose, treatment, and prognosis is recommended.**

Acute Radiation Syndrome

Acute radiation syndrome (ARS) is an acute illness caused by irradiation of the whole body (or a significant portion of it). It follows a somewhat predictable course and is characterized by signs and symptoms which are manifestations of cellular deficiencies and the reactions of various cells, tissues, and organ systems to ionizing radiation.

Immediate, overt manifestations of the acute radiation syndrome require a large (i.e., hundreds of rem, usually whole-body) dose of penetrating radiation delivered over a short period of time. Penetrating radiation comes from a radioactive source or machine that emits gamma rays, X-rays, or neutrons. The signs and symptoms of this syndrome are non-specific and may be indistinguishable from those of other injuries or illness.

The ARS is characterized by four distinct phases: a prodromal period, a latent period, a period of illness, and one of recovery or death. During the prodromal period patients might experience loss of appetite, nausea, vomiting, fatigue, and diarrhea; after extremely high doses, additional symptoms such as fever, prostration, respiratory distress, and hyperexcitability can occur. However, all of these symptoms usually disappear in a day or two, and a symptom-free, latent period follows, varying in length depending upon the size of the radiation dose. A period of overt illness follows, and can be characterized by infection, electrolyte imbalance, diarrhea, bleeding, cardiovascular collapse, and sometimes short periods of unconsciousness. Death or a period of recovery follows the period of overt illness.

In general, the higher the dose the greater the severity of early effects and the greater the possibility of late effects.

Depending on dose, the following syndromes can be manifest:

- **Hematopoietic syndrome** - characterized by deficiencies of WBC, lymphocytes and platelets, with immunodeficiency, increased infectious complications, bleeding, anemia, and impaired wound healing.

- **Gastrointestinal syndrome** - characterized by loss of cells lining intestinal crypts and loss of mucosal barrier, with alterations in intestinal motility, fluid and electrolyte loss with vomiting and diarrhea, loss of normal intestinal bacteria, sepsis, and damage to the intestinal microcirculation, along with the hematopoietic syndrome.
- **Cerebrovascular/Central Nervous System syndrome** - primarily associated with effects on the vasculature and resultant fluid shifts. Signs and symptoms include vomiting and diarrhea within minutes of exposure, confusion, disorientation, cerebral edema, hypotension, and hyperpyrexia. Fatal in short time.
- **Skin syndrome** - can occur with other syndromes; characterized by loss of epidermis (and possibly dermis) with "radiation burns."

Initial Emergency Management:

- If trauma is present, treat.
- If external contaminants are present, decontaminate.

Diagnosis:

- History of exposure - consider acute radiation syndrome in the differential diagnosis if there is:
- a history of a known or possible radiation exposure (for example, entering an irradiation chamber when the source is unshielded)
- a history of proximity to an unknown (usually metallic) object with a history of nausea and vomiting, especially if n/v are unexplained by other causes
- a tendency to bleed (epistaxis, gingival bleeding, petechiae) and/or respiratory infection with neutropenia, lymphopenia, and thrombocytopenia, with history of nausea and vomiting two to three weeks previously
- epilation, with a history of nausea and vomiting two to three weeks previously
- Symptom - type of symptom, time of onset, severity, and frequency.
- Clinical lab - STAT CBC with differential. Repeat in 4-6 hours, then every 6 to 8 hours for 24 to 48 hours. Look for a drop in the absolute lymphocyte count if the exposure was recent (see diagram). If the initial WBC and platelet counts are abnormally low, consider the possibility of exposure a few days to weeks earlier.

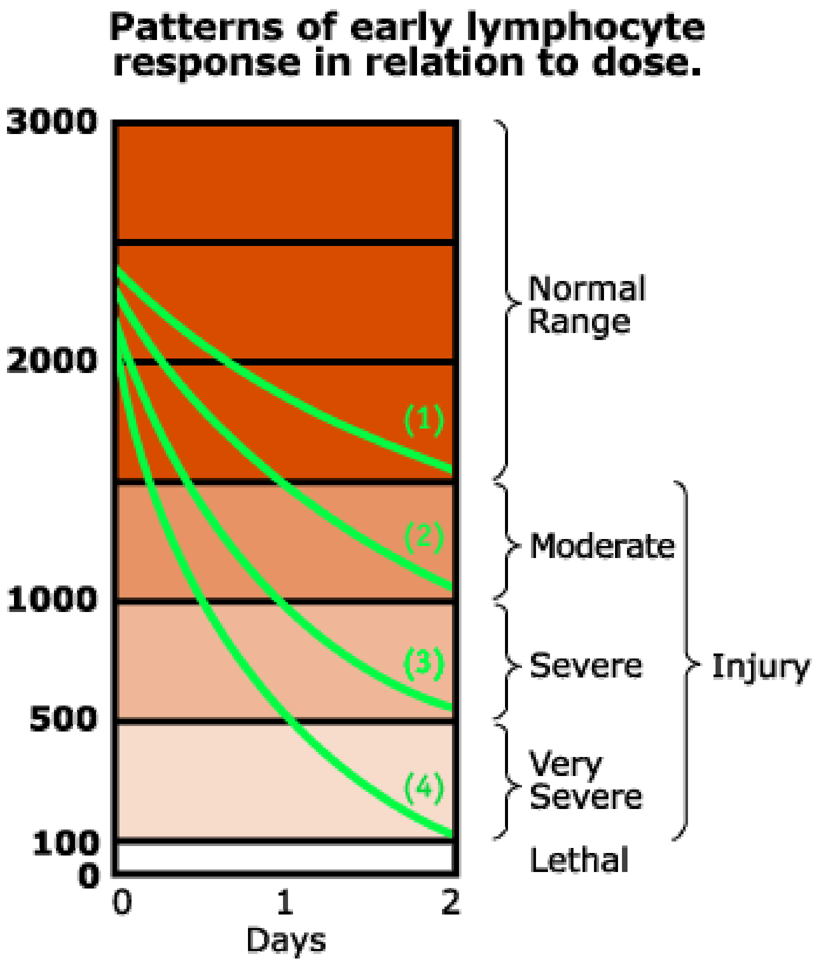


Figure. Classical Andrews lymphocyte depletion curves and accompanying clinical severity ranges. According to the data presented in this paper, curse 1-4 correspond roughly to the following whole-body doses: curve 1 - 3.1 Gy; curve 2 - 4.4 Gy; curve 3 - 5.6 Gy; curve 4 - 7.1 Gy.

From Goans, Ronald E., Holloway, Elizabeth C., Berger, Mary Ellen, and Ricks, Robert C. "Early Dose Assessment Following Severe Radiation Accidents," Health Physics *72(4): 1997.*

Acute Radiation Syndrome: Dose Less Than 2 Gy

Nausea and vomiting due to radiation are seldom experienced unless the exposure has been at least 0.75 to 1 Gy (75-100 rads) of penetrating gamma or X-rays and it has occurred within a matter of a few hours or less. The prospective patient who has been asymptomatic within the past 24 hours will most certainly have had less than 0.75 Gy of whole-body exposure. Hospitalization generally will be unnecessary if the dose has been less than 2 Gy (200 rads).

Management of ARS (dose <2 Gy):

- Close observation and frequent CBC with differential.
- Outpatient management may be appropriate.
- Provide instructions regarding home care.

Acute Radiation Syndrome: Dose Greater Than 2 Gy (200 rad)

Signs and symptoms become increasingly severe with dose.

Hematopoietic Syndrome:

- The prodromal phase - nausea, vomiting and anorexia within a few hours at the higher dose levels, or after 6 to 12 hours at the lower dose levels. Lasts 24 to 48 hours, after which time the patient is asymptomatic and may feel well. The absolute lymphocyte count will fall; a stress response of WBC may be present.
- The latent phase - lasts a few days to as long as 2 to 3 weeks at the lower dose levels. The patient is asymptomatic but CBCs will show characteristic changes in the blood elements, with lymphocyte depression and gradual decrease in neutrophil and platelet counts.
- A bone marrow depression phase requires sophisticated treatment. Infection and hemorrhage could occur when white cell and platelet counts become critically low.
- The recovery phase - stem cells in the bone marrow are never completely eradicated at 2 to 10 Gy (200 to 1000 rads); some may replicate and eventually produce sufficient blood elements. Supportive therapy is required.

Gastrointestinal Syndrome:

- Over 10 Gy (1000 rads) - this syndrome is distinguishable from the hematopoietic syndrome by the immediate, prompt and profuse onset of nausea, vomiting and diarrhea, followed by a short latent period. GI symptoms recur and lead to marked dehydration, and vascular effects. The GI mucosa becomes increasingly atrophic, and massive amounts of plasma are lost to the intestine. Massive denuding of the GI tract and accompanying septicemia and dehydration can occur. If the patient survives long enough, depression of the hematopoietic system occurs and complicates the clinical course.

Cardiovascular Syndrome:

- Over 30 Gy (3000 rads), an extremely high dose, to the whole-body. Always fatal, there is immediate nausea, vomiting, anorexia and prostration, and irreversible hypotension; blood pressure will be markedly unstable. Within hours after exposure, the victim will be listless, drowsy, tremulous, convulsive, and ataxic. Death most likely will occur within a matter of days.

Management of Acute Radiation Syndrome (Dose >2 Gy)

Initial management:

- Vomiting - use selective blocking of serotonin 5-HT_3 receptors or use 5-HT_3 receptor antagonists.
- Consider initiating viral prophylaxis.
- Consider tissue, blood typing.
- Treat trauma.
- Consider prompt consultation with hematologist and radiation experts, re: dosimetry and prognosis, use of colony stimulating factors, stem cell transfusion, and other treatment options.
- Draw blood for chromosome analysis; use heparinized tube.
- Note areas of erythema and record on body chart. If possible, take photographs.

Begin, as indicated:

- SUPPORTIVE CARE in a CLEAN environment (reverse isolation).
- Prevention and treatment of infections.
- Stimulation of hematopoiesis (use of growth factors, i.e., GCSF, GMCSF, interleukin 11).
- Stem cell transfusions: cord blood, peripheral blood, or bone marrow. Platelet transfusions if bleeding occurs or if platelet count too low.
- Psychological support.
- Observe carefully for erythema (document locations), hair loss, skin injury, mucositis, parotitis, weight loss, and/or FEVER.

- Consultation with experts in radiation accident management is encouraged.

Treatment of Internal Contamination

Once radioactive materials cross cell membranes, they are said to be incorporated. Incorporation is a time-dependent, physiological phenomenon related to both the physical and chemical natures of the contaminant. Incorporation can be quite rapid, occurring in minutes, or it can take days to months. Thus, time can be critical and prevention of uptake is urgent. Several methods of preventing uptake (e.g., catharsis, gastric lavage) might be applicable and can be prescribed by a physician. Some of the medications or preparations used in decorporation might not be available locally and should be stocked when a decontamination station is being planned and equipped. Examples of specific agents used for selected radionuclides can be seen in the table below. Expert guidance is available from NCRP 65, poison control centers, or call REAC/TS (865-576-3131) or the 24-hour emergency number (865-576-1005).

If internal contamination is suspected or has occurred, the physician or radiation safety officer should request samples of urine, feces, vomitus, wound secretion, etc. Whole-body counting and radioassay can help evaluate the magnitude of the problem and the effect of any treatment. The contaminated patient admitted with an airway or endotracheal tube must be considered to be internally contaminated.

Suggested Treatment for Select Radionuclides

Radionuclide	Medication	For Ingestion/Inhalation	Principle of Action
Iodine	KI (potassium iodide)	130 mg (tabl) stat, followed by 130 mg q.d. x 7 if indicated	Blocks thyroid deposition
Rare earths Plutonium Transplutonics Yttrium	Zn-DTPA Ca-DTPA	1 gm Ca-DTPA (Zn-DTPA) in 150-250 ml 5 percent D/W IV over 60 minutes	Chelation
Uranium	Bicarbonate	2 ampules sodium bicarbonate (44.3 mEq each; 7.5%) in 1000 cc normal saline @ 125 cc/hr; alternately, oral administration of two bicarbonate tablets every 4 hours until the urine reaches a pH of 8-9	Alkalinization of urine; reduces chance of acute tubular necrosis
Cesium Rubidium Thallium	Prussian Blue [Ferrihexacyano-Ferrate (II)]	1 gm with 100-200 ml water p.o. t.i.d. for several days	Blocks absorption from GI tract and prevents recycling.
Tritium	Water	Force fluids	Isotopic dilution

Information on Zn-DTPA, Ca-DTPA and Prussian Blue is provided at the end of this manual.

MANAGING EMERGENCY CARE OF PATIENTS CONTAMINATED WITH RADIOACTIVE MATERIALS

Notification and Accident Verification

When the hospital receives a call that a radiation accident victim is to be admitted, a planned course of action should be followed. The individual receiving the call should get as much information as possible, including the following:

1. Number of accident victims
2. Each victim's medical status and mechanism of injury
3. If victims have been surveyed for contamination
4. Radiological status of victims (exposed vs. contaminated)
5. Identity of contaminant, if known
6. Estimated time of arrival

If any doubt about contamination exists, assume the victim is contaminated until proven otherwise. Advise ambulance personnel of any special entrance to the emergency department for the radiation accident victim. If the accident notification comes from a source other than usual emergency communications, get a call-back number and verify the accident prior to assembling the radiological emergency response team and preparing for patient admission.

The Radiological Emergency Response Team

Each member of this team should be familiar with the hospital's written plan and be required to participate in scheduled drills. More frequent drills (quarterly or semiannually) should be considered by subgroups such as decontamination, triage, or radiological monitoring. Special training must be instituted to accommodate staff turnover. Training should also be part of the hospital inservice program and should include EMTs and paramedics since they play an important role in assisting the emergency department staff through notification procedures before arrival and proper transport of radiation accident victims.

The Goals of Contamination Control are to Prevent the Spread of Radioactive Materials From:

1. The patient. In most circumstances the victim will be the source of the contamination; however, in rescue and extrication, some contamination may have been transferred to others.

2. The rescue personnel

3. The gurney and equipment used in patient care (stethoscope, BP cuff, etc.)

4. The ambulance

This contamination can be transferred to:

1. Care providers as they touch or move the patient to correct the medical problem

2. The equipment used to assess the patient's condition and to treat the medical emergency

3. The surrounding area (treatment gurney, floor, etc.)

In rare cases where dust or powders are present, the air could contain radioactive particles

Radiological Emergency Response Team	
Personnel Role	**Function**
Team coordinator	Leads, advises, and coordinates
Emergency physician	Diagnoses, treats, and provides emergency medical care; can also function as team coordinator or triage officer
Triage officer	Performs triage
Nurse	Assists physician with medical procedures, collection of specimens, radiological monitoring, and decontamination; assesses patient's needs and intervenes appropriately
Technical recorder	Records and documents medical and radiological data
Radiation safety officer	Supervises all aspects of monitoring and contamination control
Radiation safety personnel	Monitors patient and area and advises on contamination and exposure control; maintains survey equipment
Public information officer	Releases accident information to public media
Administrator	Coordinates hospital response and assures normal hospital operations
Security personnel	Secures the radiation emergency area and controls crowds
Maintenance personnel	Aids in preparation of the radiation emergency area for contamination control
Laboratory technician	Provides routine clinical analysis of biological samples

Techniques of Contamination Control

4. Set up a controlled area large enough to hold the anticipated number of victims.

5. Prevent tracking of contaminants by covering floor areasand monitoring at exits of controlled areas.

6. Restrict access to the controlled area.

7. Monitoring *anyone* or *anything* leaving the controlled area.

8. Use strict isolation precautions, including protective clothing and double bagging.

9. Use a buffer zone or secondary control line for added security.

10. Control waste by using large, plastic-lined containers for clothing, linens, dressings, etc.

11. Control ventilation.

12. Change instruments, outer gloves, drapes, etc., when they become contaminated.

13. Use waterproof materials to limit the spread of contaminated liquids; for example, waterproof aperture drapes.

If Radioactive Contamination Is Discovered After Patient Has Been Admitted

1. Continue attending to the patient's medical needs.

2. Secure entire area where victim and attending staff have been.

3. Do not allow anyone or anything to leave area until cleared by the radiation safety officer.

4. Establish control lines, and prevent the spread of contamination.

5. Completely assess patient's radiological status.

6. Personnel should remove contaminated clothing before exiting area; they should be surveyed, shower, dress in clean clothing, and be resurveyed before leaving area.

Response Team Preparation

Protective clothing

The purpose of protective clothing is to keep bare skin and personal clothing free of contaminants. Members of the radiological emergency response teams should dress in surgical clothing (scrub suit, gown, mask, cap, eye protection, and gloves). Waterproof shoe covers also should be used. All open seams and cuffs should be taped using masking or adhesive tape. Fold-over tabs at the end of each taped area will aid removal. Two pairs of surgical gloves should be worn. The first pair of gloves should be under the arm cuff and secured by tape. The second pair of gloves should be easily removable and replaced if they become contaminated. A radiation dosimeter should be assigned to each team member and attached to the outside of the surgical gown at the neck where it can be easily removed and read. If available, a film badge or other type of dosimeter can be worn under the surgical gown. A waterproof apron can also be worn by any member of the team using liquids for decontamination purposes.

This protective clothing is effective in stopping alpha and some beta particles but not gamma rays. Lead aprons, such as those used in the x-ray department, are not recommended since they give a false sense of security -- they will not stop most gamma rays.

Preparing the Treatment Area for Contamination Control

If possible, select a treatment room near an outside entrance. Clear the area of visitors and patients. Remove or cover equipment that will not be needed during emergency care of the radiation accident victim.

Several large plastic-lined waste containers will be needed. The treatment table should be covered with several layers of waterproof, disposable sheeting. Plastic bags in all sizes will be needed and should be readily available.

Survey instruments should be checked and ready for use before the patient arrives. Background radiation levels should be documented.

The treatment team should be prepared to meet the patient at the ambulance where the patient can be transferred to the prepared treatment gurney.

Covering floor areas

Rolls of brown wrapping paper or butcher paper three to four feet wide can be unrolled to make a path from the ambulance entrance to the decontamination room. Ordinary cloth sheets or square absorbent pads can be used if paper is unavailable. Whatever the floor covering, *it should be taped securely to the floor*. This route should then be roped off and marked to prevent unauthorized entry. The floor of the decontamination room or treatment area should be covered in a similar way if time allows. This will make cleanup of the area easier.

A control line should be established at the entrance to the decontamination room. A wide strip of tape on the floor at the entrance to the room should be marked clearly to differentiate the controlled (contaminated) from the non-controlled (uncontaminated) side.

Control ventilation

While it may be desirable that the room, or rooms, have either a ventilation system that is separate from the rest of the hospital or a means of preventing the unfiltered exhaust air of the radiation emergency area from mixing with the air that is distributed to the rest of the hospital, there is very little likelihood that contaminants will become suspended in air and enter the ventilation system. Hence, no special precautions are advised.

(Ref.: AMA. A Guide to the Hospital Management of Injuries Arising from Exposure to or Involving Ionizing Radiation. 1984).

HOSPITAL EMERGENCY CARE OF THE RADIATION ACCIDENT PATIENT

Patient arrival and triage

Meet the radiation accident victim at the ambulance or at a triage area established near the treatment area. Instruct EMS personnel to stay with their vehicle until they, their vehicle, and equipment are surveyed and released by a radiation safety officer.

During triage, consideration is given to medical and radiological problems. **Serious medical problems always have priority over radiological concerns**, and immediate attention is directed to life-threatening problems. Radiation injury rarely causes unconsciousness or immediate visible signs of injury and is not immediately life threatening; therefore other causes of injury or illness **must** be considered.

Noncontaminated patients are admitted to the usual treatment area.

Contaminated patients are admitted to a specially prepared area. When in doubt, a critically injured patient should be taken immediately into the prepared area. If the victim's condition allows, an initial, **brief** radiological survey can be performed to determine if the victim is contaminated. Any radiation survey meter reading above background radiation levels indicates the possibility of contamination. A more thorough survey will be performed once life-threatening problems are addressed.

The victim's contaminated clothing should be removed before arrival at the hospital (at the accident scene), if this can be accomplished without causing harm or delay. Otherwise, the clothing should be removed as promptly as possible (without compromising life or limb), using care to avoid spread of any contaminants embedded in or on the clothing. Clothing, and any accompanying sheets, blankets, etc. should be placed in a plastic bag. Care-givers should change gloves after handling clothing or other potentially contaminated items.

Assessment and treatment of the noncontaminated patient

Noncontaminated individuals can be cared for like any other emergency case. A specially prepared treatment area is not needed. Following attention to medical needs, question the patient to determine the possibility of radiation exposure from an external source. Remember, the victim of exposure without contamination poses no radiological hazard to anyone. If exposure is known or suspected, a stat CBC should be ordered with particular attention given to determining the absolute lymphocyte count. Be sure to record the time the blood sample is taken. For differential diagnosis, refer to acute radiation injury.

Assessment and treatment of the contaminated patient

Contaminated patients can have radioactive materials deposited on skin surfaces, in wounds, or internally (ingested, inhaled, or absorbed). Reassessment of the contaminated patient's airway, breathing, and circulation are done in the decontamination room prior to attention to the patient's radiological status. Level of consciousness and vital signs are assessed promptly and the patient's condition is stabilized. After examining the entire patient and identifying all injuries, a complete radiological survey should be done.

The patient should be questioned about allergies, currently used medications, any history of chronic or recent illness, and **recent nuclear medicine tests**. The patient's level of anxiety should be noted, and psychological support offered. A complete and detailed medical, occupational, and accident history should be taken, and a physical examination completed.

Certain clinical and radiological laboratory analyses (see Radiological and Clinical Laboratory Assessments section below) are essential to the care of the radiation accident patient. These laboratory tests are done to assess the biological effects of radiation injury; to identify abnormalities that might complicate treatment; to locate, identify, and quantify radionuclide contamination; and to provide information useful in accident analysis.

Radiological and clinical laboratory assessments

All samples ***must*** be placed in separate, labeled containers that specify name, date, time of sampling, area of samples, and size of area samples. It is suggested that blood, urine, feces, or other samples taken in the emergency treatment period be retained for subsequent investigation. Appropriate advice (legal, radiation safety, etc.) should be obtained regarding the storage and disposition requirements of collected samples.

Samples Needed	Why?	How?
***In all cases of radiation injury*:**		
CBC and differential STAT (follow with absolute lymphocyte counts every 6 hours for 48 hours when history indicates possibility of total-body irradiation)	To assess the radiation dose; initial counts establish a baseline, subsequent counts reflect the degree of injury	Choose a noncontaminated area for veni-puncture; cover puncture site after collection
Routine urinalysis	To determine if kidneys are functioning normally and establish a baseline of urinary constituents; especially important if internal contamination is a possibility	Avoid contaminating specimen during collection; if necessary, give the patient plastic gloves to wear for collection of specimen; label specimen "Number 1," with date and time
***When external contamination is suspected*:**		
Swabs from body orifices	To assess possibility of internal contamination	Use separate saline- or water- moistened swabs to wipe the inner aspect of each nostril, each ear, mouth, etc.
Wound dressing and/or swabs from wounds	To determine if wounds are contaminated	Save dressings in a plastic bag. Use moist or dry swabs to sample secretions from each wound, or collect a few drops of secretion from each using a dropper or syringe; for wounds with visible debris, use applicator or long tweezers or forceps to transfer samples to specimen containers which are placed in lead storage containers (pigs)
***When internal contamination is suspected*:**		
Urine: 24-hour specimen x 4 days	Body excreta may contain radionuclides if internal contamination has occurred	Use 24-hour urine collection container
Feces x 4 days		

Decontamination of the contaminated patient

Good judgment is essential in determining decontamination priorities. Since some radioactive materials are corrosive or toxic because of their chemical properties, medical attention might have to be directed first to a non-radiological problem if radioactive materials are components of acids, fluorides (uranium hexafluoride-UF_6), mercury, lead, or other compounds.

In general, contaminated wounds and body orifices are decontaminated first, followed by areas of highest contamination levels on the intact skin. The purpose of decontamination is to prevent or reduce incorporation of the material (internal contamination), to reduce the radiation dose from the contaminated site to the rest of the body, to contain the contamination, and to prevent its spread. Please note that frequent glove changes will be necessary.

Treatment of contaminated wounds

In a contamination accident, any wound must be considered contaminated until proven otherwise and **should be decontaminated prior to decontaminating intact skin**. When wounds are contaminated, the physician must assume that uptake (internal contamination) has occurred. Appropriate action is based on half-life, radiotoxicity, and the amount of radioactive material. It is important to consult experts as soon as possible and to initiate measures that prevent or minimize uptake of the radioactive material into body cells or tissues.

Contaminated wounds are first draped, preferably with a waterproof material, to limit the spread of radioactivity. Wound decontamination is accomplished by gently irrigating with saline or water. More than one irrigation is usually necessary. The wound should be monitored after each irrigation. Contaminated drapes, dressings, etc., should be removed before each monitoring for accurate results. When monitoring contaminated wounds or irrigation fluids, gamma radiation is easily detected while beta radiation may prove more difficult to detect. Without special, highly sophisticated wound probes, alpha contamination will not be detected. Following repeated irrigations, the wound is treated like any other wound. If the preceding decontamination procedures are not successful, and the contamination level is still seriously high, conventional debridement of the wound must be considered. Excision of vital tissue should not be initiated until expert medical or health physics advice is obtained. Debrided or excised tissue should be retained for health physics assessment.

Embedded radioactive particles, if visible, can be removed with forceps or by using a water-pik. Puncture wounds containing radioactive particles, especially in the fingers, can be decontaminated by using an "en bloc" full thickness skin biopsy using a punch biopsy instrument.

After the wound has been decontaminated, it should be covered with a waterproof dressing. The area around the wound is decontaminated as thoroughly as possible before suturing or other treatment.

Contaminated burns (chemical, thermal) are treated like any other burn. Contaminants will slough off with the burn eschar. However, dressings and bed linens can become contaminated and should be handled appropriately.

Decontamination of body orifices

Contaminated body orifices, such as the mouth, nose, eyes, and ears need special attention because absorption of radioactive material is likely to be much more rapid in these areas than through the skin.

If radioactive material has entered the oral cavity, encourage brushing the teeth with toothpaste and frequent rinsing of the mouth. If the pharyngeal region is also contaminated, gargling with a 3-percent hydrogen peroxide solution might be helpful. Gastric lavage may also be used if radioactive materials were swallowed. Contaminated eyes should be rinsed by directing a stream of water from the inner canthus to the outer canthus of the eye while avoiding contamination of the nasolacrimal duct. Contaminated ears require external rinsing, and an ear syringe can be used to rinse the auditory canal, provided the tympanic membrane is intact.

External contamination

Decontamination of the intact skin is a relatively simple procedure. Complete decontamination, which returns the area to a background survey reading, is not always possible because some radioactive material can remain fixed on the skin surface. Decontamination should be only as thorough as practical.

Decontamination should begin with the least aggressive method and progress to more aggressive ones. Whatever the procedure, take care to limit mechanical or chemical irritation of the skin. The simplest procedure is to wash the contaminated area gently under a stream of water (do not splash) and scrub at the same time using a soft brush or surgical sponge. Warm, never hot, tap water is used. Cold water tends to close the pores, trapping radioactive material within them. Hot water causes vasodilation with increased area blood flow, opens the pores, and enhances the chance of absorption of the radioactive material through the skin.

Aggressive rubbing tends to cause abrasion and erythema and should be avoided.

If washing with plain water is ineffective, a mild soap (neutral pH) or surgical scrub soap can be used. The area should be scrubbed for 3 to 4 minutes, then rinsed for 2 to 3 minutes and dried, repeating if necessary. Between each scrub and rinse, check the contaminated area to see if radiation levels are decreasing. Sodium hypochlorite, diluted 1 to 10 with water, is an effective decontamination agent. A mildly abrasive soap (a 1 to 1 mixture of powdered detergent and cornmeal mixed with water into a paste) can be used for calloused areas. **The decontamination procedure stops when the radioactivity level cannot be reduced to a lower level.** Expert advice might be needed to determine an appropriate stopping point. Contaminated hairy areas can be shampooed several times. Contaminated hair can be clipped if shampooing is ineffective. Shaving should be avoided since small nicks or abrasions can lead to internal contamination. When shampooing the head, avoid getting any fluids into the ears, eyes, nose, or mouth.

Ambulatory patients with localized contamination can be decontaminated using a sink or basin. If extensive body areas are contaminated, the patient can be showered under the direction or with the assistance of a radiation safety officer. Caution the patient to avoid splashing water into the eyes, nose, mouth, or ears. Repeated showers might be necessary, and clean towels provided for drying after each shower. Again, decontamination should be as thorough as practical.

Although it may be desireable that the wastewater from decontamination procedures be retained and analyzed before being discharged into the sanitary sewer, this requirement should not be mandatory. Furthermore, the installation of an elaborate holding system is not likely to be justified because of the infreqency of the event. The welfare of the patient should come first, and the physician should feel free to use whatever facilities are readily available to accomplish that end. Any radiation hazard to the general public will be virtually eliminated when the inherently small and infrequent volume of radioactive waste is mixed with and diluted by other sewage effluents of the hospital and community (AMA, 1984).

Patient comfort and emotional support

A patient involved in a radiation accident needs explanations of procedures and actions being taken (isolation, use of survey meters, taking of samples, decontamination, etc.) in the radiation emergency area. A knowledgeable person should answer the patient's questions and provide reassurance. For example, explain use of protective clothing and surgical masks during treatment. Following initial care and treatment, someone with a knowledge of radiation effects should spend adequate time answering the patient's questions.

Preferably, this person should be the attending physician who continues to treat the patient until discharge. Reporters and news-hunters should get their reports from the hospital's public information officer.

Patient safety

Routine precautions for patient safety should not be forgotten. Be especially alert for potential falls or slips on wet floors, excessive heating or chilling, and electrical hazards.

Documentation

In addition to routine medical records, note survey readings, samples taken (and time), descriptions of the accident, and the effectiveness of decontamination. Take care to note pre-existing conditions such as rashes, healing wounds, or scars. This information will be extremely valuable to medical consultants and health physicists in reconstructing the accident accurately and making a prognosis.

Post-emergency patient transfer

A final complete-body survey is performed following decontamination procedures. A new floor covering is laid from the clean area to the patient stretcher. A clean stretcher is brought in, the patient is transferred to it by clean attendants (those involved in the decontamination procedure may now be contaminated), and the patient is wheeled to the door. After the radiation safety officer makes a final check of the patient and the stretcher (especially the wheels), the patient is taken from the room.

Staff exit from the controlled area

Each member of the decontamination team goes to the control line and removes his protective clothes as described below:

1. Remove outer gloves first, turning them inside-out as they are pulled off.

2. Give dosimeter to radiation safety officer.

3. Remove all tape at trouser cuffs and sleeves.

4. Remove outer surgical gown, turning it inside-out -- avoid shaking.

5. Pull surgical trousers off over shoe covers.

6. Remove head cover and mask.

7. Remove shoe cover from one foot and let radiation safety officer monitor shoe; if shoe is clean, step over control line, then remove other shoe cover and monitor other shoe.

8. Remove inner gloves.

9. Do total-body radiological survey of each team member.

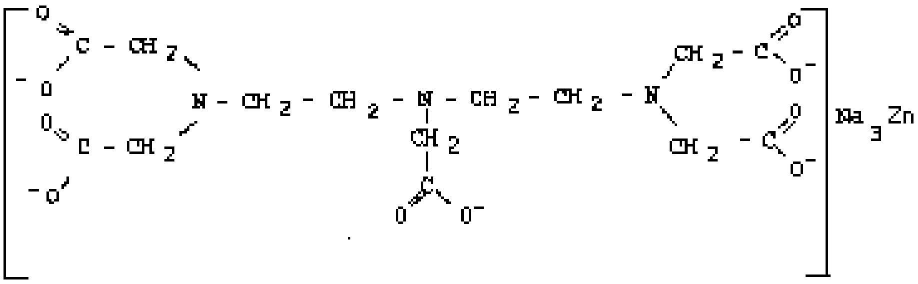
10. Take shower.

After staff exit, the decontamination room should be secured and a sign reading **"CAUTION -- CONTROLLED AREA -- DO NOT ENTER"** should be posted. Unless it is needed for emergency medical reasons, the decontamination room remains secured until it can be checked and decontaminated, if necessary, by the radiation safety officer or other health physics expert.

Zn-DTPA (Trisodium zinc diethylenetriaminepentaacetate)

INFORMATIONAL MATERIAL

PACKAGE INSERT



DESCRIPTION

IND 14,603, Trisodium zinc diethylenetriaminepentaacetate (Zn-DTPA), is a zinc salt of DTPA. It has been used in the U.S. as a chelating agent for plutonium and other transuranic elements such as americium, californium, and curium. DTPA is also commonly used in lesser concentrations as a chelating vehicle in FDA-approved nuclear medicine studies.

Zn-DTPA is distributed by Oak Ridge Associated Universities (ORAU) under contract with the U.S. Department of Energy (DOE), Contract No. DE-AC05-76OR00033. ORAU manages the FDA Investigational New Drug (IND) authorizations for Zn-DTPA and the analogous Ca-DTPA for DOE. The current supply of Ca-DTPA has been purchased from Heyl GmbH, Berlin, Germany and has been tested extensively by them for chemical stability and chemical purity and by an independent testing company for pyrogenicity. The drug is supplied as one gram in 5 ml of diluent. This formulation has been approved by the US FDA and meets the standards of both the United States Pharmacopeia (USA 23) and the European pharmacopeia (Ph.Eur).

CLINICAL PHARMACOLOGY

DTPA belongs to the group of synthetic polyamino polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions. Zn-DTPA removes toxic metals by exchanging its cations for metals that form more stable complexes with the DTPA ligand. The complex is then excreted in the urine.

The plasma half-life of DTPA is 20-60 minutes. Almost the entire administered dose is excreted in 12 hours, with only a small amount bound to plasma proteins, having a half-life of >20 hours. DTPA undergoes only a minimal amount of metabolic change in the body. Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Following intravenous administration, Zn-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissue. No accumulation of DTPA in specific organs has been observed. There is little or no binding of the chelate by the renal parenchyma, and it is promptly cleared from the body by glomerular filtration. Tubular excretion has not been observed. Although clearance of the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance. In stool samples tested with radioactively marked chelating agents, only a very small amount of radioactivity (<3%) was detected.

One patient with chronic Ca/Zn-DTPA administration for over 3 years was assayed for 24 elements including almost all of the trace metals recognized as essential for good health. Zinc was found to be the only metal excreted more rapidly than normal.[5] The 132 mg of zinc contained in 1 g of Zn-DTPA compensates for the loss of 18 mg of zinc that was found to be associated with the injection of 1 g of DTPA salt.

*****_Reviewed and approved for continuation for 12 months by the ORAU/ORNL Institutional Review Board, December 1, 1999._

INDICATIONS AND USAGE

Ca-DTPA and Zn-DTPA effectively chelate several transuranium ions (plutonium, americium, berkelium, curium, and californium). Their clinical use has been primarily for treatment of internal contamination with plutonium and americium. One patient contaminated with more than 1 mCi of americium had 99% of the total body burden removed with prolonged therapy over 4 years with a combination of Ca-DTPA/Zn-DTPA therapy.

The efficacy of Ca-DTPA and/or Zn-DTPA treatment for internal contamination with the actinides is good for soluble salts, such as the nitrate or chloride, but is essentially nil for highly insoluble compounds, such as the high-fired oxide. The same effects are noted experimentally when a soluble (monomeric) form of plutonium is administered that gradually converts to less soluble (polymeric) forms as it is distributed and deposited in various tissues in the body. Thus, chelation is highly dependent not only on the actual metal, but also on the chemical and physical characteristics of the compound at the time of DTPA administration.

Zn-DTPA is initially 10 times less effective than Ca-DTPA for initial chelation of transuranics; therefore, Ca-DTPA should be used whenever larger body burdens of transuranics are involved. Ca-DTPA is the drug of choice for initial patient management unless contraindicated. After approximately 24 hours, however, Zn-DTPA is for all practical purposes as effective as Ca-DTPA, since the efficiency of both agents is about the same. The comparable efficacy, coupled with its lesser toxicity, makes Zn-DTPA the preferred agent for protracted therapy.

CONTRAINDICATIONS

Zn-DTPA should not to be used as a chelator for uranium or neptunium. Internal contamination with uranium is currently treated by alkalizing the urine with bicarbonate in order to promote excretion. DTPA has also been postulated to form an unstable complex with neptunium, which may increase bone deposition of this actinide.[6]

WARNINGS AND PRECAUTIONS

1. Fractionation of the recommended 1 g dose (several smaller doses per day) is not recommended, although Zn-DTPA does not appear to have the increased toxicity of Ca-DTPA (associated with fractionated treatment).

2. Blood pressure should be monitored closely during infusion.

3. Discontinue the drug if diarrhea occurs.

Usage in Pregnancy - Pregnancy Category C -

The chelates do not significantly cross placental barriers. There have been several studies indicating the lack of teratogenic effects by Zn-DTPA at doses up to several times the human intravenous dose of 0.0287 mmol/kg. In these experiments, Zn-DTPA did not show toxicity during pregnancy as did Ca-DTPA. In pregnant mice given a daily dose of 11.5 mmol/kg (400 times the human dose), the only fetal effect observed was a slight reduction in the average birth weight.[7] Zn-DTPA is therefore preferred over Ca-DTPA in pregnancy and should be used, if available, to treat a pregnant female with internal transuranic contamination. However, there are no adequate and well-controlled studies of Zn-DTPA in pregnant women. The potential benefits of transuranic decorporation must therefore be weighed against the risk to the fetus.

ADVERSE REACTIONS

No serious toxicity in humans has been reported as a result of over 1000 Zn-DTPA administrations in recommended doses. When given repeatedly, with short intervals for recovery, Zn-DTPA treatment may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours.

In one patient, long-term, low-dose combination Ca/Zn-DTPA administration was performed using six different schedules: 1 g Ca-DTPA/24h, 1 g Ca-DTPA/12h, 1 g Zn-DTPA/12h, 1 g Zn-DTPA/8h, 1 g Zn-DTPA/12h, 0.5 g Zn-DTPA/12h, 1 g Zn-DTPA/24h and 1 g Zn-DTPA three times a week. After 939 days of such administration, there were no adverse effects observed.[2]

OVERDOSAGE

Zn-DTPA is some 30 times less toxic than Ca-DTPA to mice when given daily at high doses. Acutely lethal doses of Zn-DTPA are estimated at >20 mmol/kg or 10g/kg in the adult male mouse.[7] In animal and in human studies, in contrast to experience with Ca-DTPA, there has been no observed decrease in Zn or Mn in the liver, small intestine, or in the kidneys.

DOSAGE AND ADMINISTRATION

Each dose should be 1 gram of Zn-DTPA. The route of administration may be either intravenous infusion of the undiluted solution over a period of 3-4 minutes, intravenous infusion (in 100-250 ml D_5W, Ringers Lactate, or normal saline), or inhalation in a nebulizer (1:1 dilution with water or saline). Intravenous administration should not be protracted over more than 2 hours.

Clinical experience has shown that aerosol inhalation of Zn-DTPA is more effective than intramuscular injection, apparently because distribution to the body from the lung is slower than from muscle, and results in a longer lasting plasma level. This same relationship exists when comparing the effectiveness of aerosol inhalation of Zn-DTPA to intravenous injection.

Zn-DTPA may be administered undiluted by intramuscular injection when intravenous administration is not practical, although significant pain at the injection site has resulted when this route is used. The addition of 1-2% procaine to the undiluted Zn-DTPA prior to intramuscular injection has proven to be helpful.

The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to the tissue fluids and plasma. However, a post-exposure interval >1 hour does not preclude the administration and effective action of Zn-DTPA.

Combined Ca-DTPA/Zn-DTPA Therapy Guidelines

It must be noted that this is a general guide for DTPA therapy and that treatment must be specifically tailored for individual patients. Ca-DTPA and Zn-DTPA generally can be thought of as two components of transuranic decorporation therapy. If there is any contraindication to the use of Ca-DTPA, the same dose of Zn-DTPA may be substituted.

A. On assurance that a credible incident has occurred and the exposed person(s) at risk has in all likelihood received internal transuranic contamination:

1. Obtain the patient's signature on an informed consent form for DTPA therapy (which should cover both Ca and Zn forms).

2. Obtain base-line blood and urine samples (CBC with differential, BUN, serum creatinine, urinalysis and urine radioassay).

3. Administer 1 g Ca-DTPA by the most appropriate route for the particular patient.

4. Begin collection of 24-hour urine and fecal samples for bioassay. Whole body and/or chest counting should also be performed. Blood assays may be done if the initial urinalysis was positive for transuranic contamination.

5. If long-term use of Ca-DTPA is contemplated, one should consider the use of supplemental zinc therapy (one 220-mg zinc sulfate tablet daily delivers 50 mg zinc systemically).

6. Repeat doses of 1 g Ca-DTPA or 1 g Zn-DTPA may be administered daily for up to 5 days per week if the radioassay data or history indicate the need for additional chelation. Keep in mind that the majority of patients in the past have received only one dose of DTPA.

7. Although no significant side effects of DTPA at the recommended dosage level are Known and there are no known contraindications to its use, urinalysis and complete blood counts should be done on the day following the initial treatment and as

indicated medically thereafter. The patient's pulse and blood pressure also should be monitored to determine any effect of the drug. Bioassay results and any side effects should be noted and recorded on the standard treatment form and reported to ORAU for the annual DTPA usage survey. Significant side effects should be reported promptly.

8. Additional tests may be ordered at the discretion of the investigator and with the consent of the patient.

B. Before, during and after chelation therapy, pertinent measurements for radioactivity should be made to determine the efficacy of treatment. By the fifth day, evaluate bioassay data for body-burden estimation and decide whether further chelation is necessary. If so, a Zn-DTPA treatment regimen should be implemented.

1. Begin the therapy regimen by administration of Zn-DTPA on a two-dose per week basis, 1 g Zn-DTPA per dose, until such time as excretion rate of the transuranic is not increased by Zn-DTPA administration.

2. Wait four to six months, re-establish base-line urinary excretion-rate value and give a 1 g Zn-DTPA dose by an appropriate route. Obtain bioassay or urinary excretion to determine whether the Zn-DTPA increased excretion of the contaminant.

3. If medically indicated, begin a second course of Zn-DTPA treatment on a two dose per week basis as in (1) above.

C. If bioassay data indicates that contamination was not excessive, then further chelation therapy may be discontinued at the discretion of the attending physician.

D. When the patient is released from further therapy, he/she should be followed at the routine intervals established by the occupational practice of the facility. A urinalysis is recommended at these examinations.

It is recommended that, at the time of an employment termination, the physician should forward a copy of the medical history to a physician of the patient's choice. In addition, the physician should offer the patient the opportunity to be followed medically by the DOE follow-up system. This should be done to ensure continuity of patient care if he/she should again become contaminated and require therapy at another plant site.

Patients who have received extensive chronic incorporation of transuranics require unusual therapy and will be treated largely according to the discretion of the investigator. In the past, treatment has not exceeded three 1 g doses of Zn-DTPA during any 24-hour period. Doses should be administered by the route considered most appropriate for the particular patient.

HOW SUPPLIED

Each ampule provided contains 1 g Zn-DTPA. The solution should be clear, colorless, and free of crystalline or other material. The ampules should be stored in cool place and away from sunlight.

As a part of the management of the IND for Zn-DTPA, annual quality control tests are performed on randomly selected ampules of the drug. There is no indication that deterioration, pyrogenicity, or loss of sterility occur when the ampules are stored at room temperature. However, if any problem of this nature should be observed, all co-investigators will be notified immediately. Any signs of deterioration (discoloration or cloudiness) of the solution or reaction on the part of the patient should be reported at once to one of the persons listed below.

The Food and Drug Administration (FDA) requires that the Sponsor and Manager(s) of the IND be in a position to account for all ampules sent to investigator physicians. These physicians must, therefore, set up an accounting system on the supplies of Zn-DTPA and be prepared to report their clinical experience annually, including observations on the safety and efficacy of the Zn-DTPA. The Manager(s) of the Zn-DTPA IND will contact all co-investigators in June of each year to obtain this report. These observations will be incorporated into ORAU's summary report to the FDA for the preceding 12-month period.

SUMMARY OF ADMINISTRATION

To maximize efficacy, if the patient has been injured, assure that medical treatment be initiated as soon as possible. However, delay does not preclude the use of DTPA. The patient's respiratory/hemodynamic status should also be stable prior to administration of the drug. The following guidelines are provided to facilitate rapid initiation of treatment.

1. Is it at all likely that the person has received internal contamination with plutonium, americium, berkelium, curium or californium?

2. DTPA is not currently approved for use with uranium or neptunium.

3. Obtain a history of renal, hematopoietic, bone marrow, cardiac or respiratory disorders and, if appropriate, the likelihood of pregnancy.

4. Obtain written informed consent for both Ca-DTPA and Zn-DTPA.

5. Obtain an initial 24-hour urine for radioassay and urinalysis.

6. If Ca-DTPA is contraindicated, use Zn-DTPA. Contraindications to the use of Ca-DTPA are current or past history of serious renal disease, bone marrow depression, pregnancy, or age less than 18 years.

7. Administer 1 g of Ca-DTPA or Zn-DTPA by IV push over 3-4 minutes, IV infusion in 100-250 ml Ringers Lactate, D_5W, or normal saline, or by inhalation in a nebulizer (1:1 dilution with water or saline). Administration is approved for use by IM injection, but this is not recommended because of pain considerations.

8. Blood pressure before and after DTPA administration should be routinely monitored.

9. Follow the remainder of the procedures in the Therapy Guidelines section.

Questions regarding the use of Zn-DTPA may be referred to one of the following personnel at the Oak Ridge Associated Universities, P. O. Box 117, Oak Ridge, TN 37831-0117:

Ronald E. Goans, Ph.D., M.D.
Co-principal Investigator, DTPA IND
(423) 576-4049

Robert C. Ricks, Ph.D.
Co-principal Investigator, DTPA IND
(423) 576-3131

Ronald D. Townsend, Ph.D.
Sponsor, DTPA IND
(423) 576-3300

REFERENCES

1. Breitenstein, B.D., Jr., Fry, S.A., and Lushbaugh, C.C. "DTPA therapy: The U.S. experience 1958-1987," in: *The Medical Basis of Radiation Accident Preparedness,* 2nd ed.*,* Ricks, R. and Fry, S.A. eds., Elsevier Science Publishing Co., Inc., pp. 397-406, 1990.

2. Breitenstein, B.D., "1976 Hanford americium exposure incident: Medical management and chelation therapy." *Health Physics* 45(4): 855-866, 1983.

3. Breitenstein, B.D., and Palmer, H.E. "Lifetime followup of the 1976 americium accident victim." *Radiation Protection Dosimetry* 26:317-322, 1989.

4. Bruenger, F.W., Taylor, D.M., Taylor, G.N., and Lloyd, R.D. "Effectiveness of DTPA treatments following the injection of particulate plutonium." *Int J Radiat Biol.* 60(5): 803-818, 1991.

5. Kalkwarf, D.R., Thomas, V.W., Nielson, K.K., Mauch, M. L. "1976 Hanford americium exposure incident: Urinary excretion of trace metals during DTPA treatments." *Health Physics* 45(4): 937-947, 1983.

6. Morin, M., Nenot, J.C., and Lafuma, J. "The behavior of 237-Np in the rat." *Health Physics* 24: 311-315, 1973.

7. Mays, C.W., et al., "Zn-DTPA safety in the mouse fetus." *Health Physics* 36: 526-529, 1979.

Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate)

INFORMATIONAL MATERIAL

PACKAGE INSERT

DESCRIPTION

IND 4041, Trisodium calcium diethylenetriaminepentaacetate (Ca-DTPA), is a calcium salt of DTPA. It has been used in the U.S. as a chelating agent for plutonium and other transuranic elements such as americium, californium, and curium. DTPA is also used in lesser concentrations as a chelating vehicle in FDA-approved nuclear medicine studies.

Ca-DTPA is distributed by Oak Ridge Associated Universities (ORAU) under contract with the U.S. Department of Energy (DOE), Contract No. DE-AC05-76OR00033. ORAU manages the FDA Investigational New Drug (IND) authorizations for Ca-DTPA and the analogous Zn-DTPA for DOE. The current supply of Ca-DTPA has been purchased from Heyl GmbH, Berlin, Germany and tested extensively by them for chemical stability and chemical purity and by an independent testing company for pyrogenicity. The drug is supplied as one gram in 5 ml of diluent. This formulation has been approved by the US FDA and meets the standards of both the United States Pharmacopeia (USP-23) and the European Pharmacopeia (Ph. Eur).

A series of review papers on the use of DTPA chelators (Ca-DTPA and Zn-DTPA) in decorporation therapy in major United States radiation accidents from 1958 through 1987 has recently been published.[-3]

CLINICAL PHARMACOLOGY

DTPA belongs to the group of synthetic polyamino polycarboxylic acids which form stable complexes (metal chelates) with a large number of metal ions. The drug effectively exchanges calcium for another metal of greater binding power and carries it to the kidneys where it is then excreted into the urine.[4]

The plasma half-life of DTPA is 20-60 minutes. Almost the entire administered dose is excreted in 12 hours. There is a small fraction bound to plasma proteins with a half-life >20 hours. DTPA undergoes only a minimal amount of metabolic change in the body. Only a very minor release of acetate groups has been demonstrated and splitting of ethylene groups has not been detected. Following intravenous administration, Ca-DTPA is rapidly distributed throughout the extracellular fluid space. No significant amount of DTPA penetrates into erythrocytes or other tissue. No accumulation of DTPA in specific organs has been observed. There is little or no binding of the chelate by the renal parenchyma, and it is promptly cleared from the body by glomerular filtration. Tubular excretion has not been observed. Although clearance of the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance. In stool samples tested with radioactively marked chelating agents, only a very small amount of radioactivity (<3%) was detected.

*_**Reviewed and approved for continuation for 12 months by the ORAU/ORNL Institutional Review Board, December 1, 1999.**_

Ca-DTPA can deplete the body of zinc and, to a lesser extent, manganese with repeated dosing. The amount of zinc lost is determined by the amount of DTPA and the frequency of dosage. By depletion of these essential trace metals, Ca-DTPA can then interfere with necessary mitotic cellular processes. Over longer time periods, depletion of zinc due to Ca-DTPA therapy has resulted in transient inhibition of a metalloenzyme, d-aminolevulinic acid dehydrase (ALAD), in the blood, although without observable clinical effect. Clinical zinc depletion appears to be avoidable by giving zinc replacement concomitantly with therapy.

Ca-DTPA is approximately 10 times more effective than Zn-DTPA for initial chelation of transuranics; therefore, Ca-DTPA should be used whenever larger body burdens of transuranics are involved. Ca-DTPA is the form of choice for initial patient management unless contraindicated. Approximately 24 hours after exposure, Zn-DTPA is, for all practical purposes, as effective as Ca-DTPA. This comparable efficacy, coupled with its lesser toxicity, makes Zn-DTPA the preferred agent for protracted therapy.

INDICATIONS AND USAGE

Ca-DTPA and Zn-DTPA effectively chelate several transuranium ions (plutonium, americium, berkelium, curium, and californium). Their clinical use has been primarily for treatment of internal contamination with plutonium and americium. One patient contaminated with more than 1 mCi of americium had 99% of the total body burden removed with prolonged therapy over 4 years with a combination of Ca-DTPA/Zn-DTPA therapy.[2-3]

The efficacy of Ca-DTPA and/or Zn-DTPA treatment is good for internal contamination with the soluble plutonium salts, such as the nitrate or chloride, but is essentially nil for highly insoluble compounds, such as the high-fired oxide. The same efficacy is noted experimentally when a soluble (monomeric) form of plutonium is administered that gradually converts to less soluble (polymeric) forms as it is distributed and deposited in various tissues in the body. Thus, chelation is highly dependent not only on the actual metal, but also on the chemical and physical characteristics of the compound at the time of DTPA administration. Because the efficiency of chelation decreases with time, DTPA should be given within 6 hours of exposure, if possible.

CONTRAINDICATIONS

Ca-DTPA is contraindicated for minors, pregnant women, patients with the nephrotic syndrome, and in patients with bone marrow depression. (Such patients may be treated with Zn-DTPA.) Ca-DTPA should not to be used as a chelator for uranium or neptunium. Internal contamination with uranium is currently treated by alkalizing the urine with bicarbonate in order to promote excretion. DTPA has also been postulated to form an unstable complex with neptunium, which may increase bone deposition of this actinide.[5]

WARNINGS AND PRECAUTIONS

1. Ca-DTPA treatment is contraindicated where there is known pre-existing serious kidney disease or depressed myelopoietic function (e.g., leukopenia or thrombocytopenia).
2. Kidney function should be normal. Urinalysis should be normal prior to each use. If proteinuria, hematuria or casts develop during use, discontinue drug administrations.
3. Fractionation of the recommend 1 g dose (several smaller doses per day) is not recommended.
4. Blood pressure should be monitored closely during drug infusion.
5. Discontinue the drug if diarrhea occurs.

Pregnancy Category D

Teratogenicity and fetal death have occurred in mice following five daily injections of 720-2880 μmol Ca-DTPA/kg given throughout the gestation. However, daily doses of 360 μmol Ca-DTPA/kg in mice, about 10 times the daily human dose, produced no harmful effects. Studies of 2 pregnant beagles given daily injections of Ca-DTPA at 30 μmol/kg, a daily dose comparable to 1 g in a 70 kg man, starting at 15 days of gestation until the end of pregnancy, have shown severe effects (especially brain damage in the fetuses).[6-7]

On the basis of these results and the lesser daily intake of zinc by humans compared to rats and mice, it has been postulated that some toxic effects on the human fetus might occur at the recommended daily dose levels of about 30 μmol Ca-DTPA/kg. In the same experiments, Zn-DTPA did not show similar toxicity. Zn-DTPA is preferred and should be used if available to treat a pregnant female with internal transuranic contamination, although it is doubtful that a single or even several well-spaced doses of Ca-DTPA would be harmful to the pregnant female or fetus, especially if prophylactic zinc is given.

ADVERSE REACTIONS

No serious toxicity in human subjects has been reported as a result of over 4500 Ca-DTPA administrations in recommended doses. When given repeatedly, with short intervals for recovery, Ca-DTPA treatment may cause nausea, vomiting, diarrhea, chills, fever, pruritus, and muscle cramps in the first 24 hours. Anosmia (loss of the sense of smell) was observed in one individual after 123 g of Ca-DTPA over twenty-seven months of therapy and possibly could have been related to zinc depletion. After 100 days of no further DTPA administration, the patient's sense of smell improved.

In one patient, low-dose Ca-DTPA administration of 1 g per week, showed no adverse effects after one month of such administration.[8] Urinary zinc excretion studies suggest that the zinc supply is quickly replenished during this treatment regimen and that any partial depletion of zinc stores, if it occurs at all, would be transient.

OVERDOSAGE

Studies in animals indicate that the toxicity of Ca-DTPA depends on the total dose and the dose schedule. When administered to animals in high doses (>/= 2000 µmol/kg - clinical dose range is 10-30 µmol/kg), the drug can produce severe lesions of the kidneys, intestinal mucosa, and liver, and can be lethal. Increased toxicity from fractionated dose schedules has been demonstrated in dog experiments in which injections at human dose levels, 5.8 µmol/kg of Ca-DTPA given every 5 hours, were fatal as early as four days after the onset of treatment. The most significant injury occurs in the intestinal epithelium. In rats, continuous infusion of similar total doses per day caused death in 8-14 days, but the same dose given as a single daily injection failed to elicit this response. Toxicity in these cases apparently resulted from depletion of the Zn and Mn ions needed in the enzymatic steps leading to DNA syntheses that renews the epithelial cells in the intestinal epithelium. No untoward effects in rats were noted with doses of 100 µmol Ca-DTPA given twice weekly and apparently there was no influence on Zn or Mn concentrations over a 44-week period on this dose schedule.

DOSAGE AND ADMINISTRATION

Each dose of Ca-DTPA should be 1 gram and doses should not be fractionated. The route of administration may be either slow intravenous push of the drug over a period of 3-4 minutes, intravenous infusion (1 g in 100-250 ml D_5W, Ringers Lactate, or normal saline), or inhalation in a nebulizer (1:1 dilution with water or saline). Intravenous administration should not be protracted over more than 2 hours.

Ca-DTPA may be administered undiluted by intramuscular injection when intravenous administration is not practical, although significant pain at the injection site has resulted when this route is used. The addition of 1-2% procaine to the undiluted Ca-DTPA prior to intramuscular injection has proven to be helpful.
The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval >1 hour does not preclude the administration and effective action of Ca-DTPA.

Combined Ca-DTPA/Zn-DTPA Therapy Guidelines

It should be noted that the statements above are general guidelines for DTPA therapy and that treatment must be specifically tailored for each individual patient. Ca-DTPA and Zn-DTPA may be thought of as two components of transuranic decorporation therapy. If there is any contraindication to the use of Ca-DTPA, the same dose of Zn-DTPA may be substituted.

A. On assurance that a credible incident has occurred and that the exposed person(s) at risk has, in all likelihood, received internal transuranic contamination:

1 Obtain the patient's signature on an informed consent form for DTPA therapy (which should over both Ca and Zn forms).

2 Obtain base-line blood and urine samples (CBC with differential, BUN, serum creatinine, urinalysis and urine radioassay) and as indicated medically thereafter.

3 Administer 1 g Ca-DTPA by the most appropriate route.

4 Begin collection of 24-hour urine and fecal samples for bioassay. Whole body and chest counting should also be performed. Blood assays may prove helpful if the initial urinalysis is positive for transuranic contamination.

5 If long-term use of Ca-DTPA is contemplated, one should consider the use of supplemental zinc therapy (one 220-mg zinc sulfate tablet daily delivers 50 mg zinc systematically).

6 Repeat doses of 1 g Calcium DTPA or 1 g Zn-DTPA may be administered daily for up to 5 days per week if the radioassay data or history indicate the need for additional chelation. Note that the majority of patients in the past have received only one dose of DTPA.

7 Although no significant side effects of DTPA at the recommended dosage level are known and there are no known contraindications to its use, urinalysis and complete blood counts should be done at the time of the initial treatment and as medically indicated thereafter. The patient's pulse and blood pressure also should be monitored during each drug infusion. Bioassay results and any side effects should be noted and recorded on the standard treatment form and reported to ORAU for the annual DTPA usage survey.

8 Additional tests may be ordered at the discretion of the investigator and with the consent of the patient.

B. Before, during and after chelation therapy, pertinent measurements for radioactivity should be made to determine the efficacy of treatment. By the fifth day, evaluate bioassay data for body-burden estimation and decide whether further chelation is necessary. If continued chelation therapy is needed, a Zn-DTPA treatment regimen should be implemented.

1. Begin the therapy regimen by administration of Zn-DTPA on a two-dose per week basis, 1 g Zn-DTPA per dose, until such time as excretion rate of the transuranic is not increased by Zn-DTPA administration.

2. Wait four to six months, re-establish a base-line urinary excretion-rate value and give a 1 g Zn-DTPA dose by an appropriate route. Obtain bioassay measurements to determine whether the Zn-DTPA increased excretion of the contaminant.

3. If medically indicated, begin a second course of Zn-DTPA treatment on a two dose per week basis as in (1) above.

C. Total length of chelation treatment after an accident is dictated by the magnitude of the accident and by the medical judgment of the attending physician.

D. When the patient is released from treatment, he/she should be followed at the routine intervals established by the occupational practice of the facility. A urinalysis is recommended at these examinations.

E. It is recommended that at the time of an employment termination, the treating physician should forward a copy of the medical history to a physician of the patient's choice. This should be done to ensure continuity of patient care and to assist if he/she should again become contaminated and require therapy at another plant site.

F. Patients who have received extensive chronic incorporation of transuranics require unusual therapy and will be treated largely according to the discretion of the investigator. In the past, treatment has not exceeded three 1 g doses during any 24-hour period. Doses should be administered by the route considered most appropriate for the particular patient.

HOW SUPPLIED

Each ampule contains 1 g Ca-DTPA. The solution should be clear, colorless, and free of crystalline or other material. The ampules should be stored in cool place and away from sunlight.

As a part of the management of the IND for Ca-DTPA, annual quality control tests are performed on randomly selected ampules of the drug. There is no indication that deterioration, pyrogenicity, or loss of sterility occur when the ampules are stored at room temperature. However, if any problem of this nature should be observed, all co-investigators will be notified immediately. Any signs of deterioration (discoloration or cloudiness) of the solution or reaction on the part of the patient should be reported at once to one of the persons listed below.

The Food and Drug Administration (FDA) requires that the Sponsor and Manager(s) of the IND be in a position to account for all ampules sent to investigator-physicians. It is necessary, therefore, to set up an accounting system for the supplies of Ca-DTPA and to be prepared to report each facility’s experience annually. This report should include observations on the safety and efficacy of the Ca-DTPA used according to the protocols submitted with the original request for Ca-DTPA. The Manager(s) of the Ca-DTPA IND will contact each physician/investigator in June annually to obtain a report. This report will be incorporated into ORAU's summary report to the FDA for the prior 12-month period.

SUMMARY OF ADMINISTRATION

To maximize efficacy, if the patient has been injured, assure that medical treatment be initiated as soon as possible. However, delay does not preclude the use of DTPA. The patient's respiratory/hemodynamic status should also be stable prior to administration of the drug. The following guidelines are provided to facilitate rapid initiation of treatment.

1. Is it at all likely that the person has received internal contamination with plutonium, americium, berkelium, curium or californium?

2. DTPA is not currently approved for use with uranium or neptunium.

3. Obtain a history of renal, blood, bone marrow, cardiac or respiratory disorders and, if appropriate, the likelihood of pregnancy.

4. Obtain written informed consent for both Ca-DTPA and Zn-DTPA.

5. Obtain a 24-hour urine for radioassay and for urinalysis.

6. If Ca-DTPA is contraindicated, use Zn-DTPA. Contraindications to the use of Ca-DTPA are current or past history of serious renal disease, bone marrow depression, pregnancy, or age less than 18 years.

7. Administer 1 g of Ca-DTPA or Zn-DTPA by IV push over 3-4 minutes, IV infusion in 100-250 ml D_5W, Ringers Lactate or normal saline, or by inhalation in a nebulizer (1:1 dilution with water or saline). Administration is approved for use by IM injection, but this is not recommended because of pain considerations.

8. Blood pressure before and after DTPA administration should be routinely monitored.

9. Follow the remainder of the procedures in the Therapy Guidelines section.

Questions regarding the use of Ca-DTPA may be referred to one of the following personnel at the Oak Ridge Associated Universities, P. O. Box 117, Oak Ridge, TN 37831-0117:

Ronald E. Goans, Ph.D., M.D.
Co-principal Investigator, DTPA IND
(423) 576-4049

Robert C. Ricks, Ph.D.
Co-principal Investigator, DTPA IND
(423) 576-3131

Ronald D. Townsend, Ph.D.
Sponsor, DTPA IND
(423) 576-3300

REFERENCES:

1. Breitenstein, B.D., Jr., Fry, S.A. and Lushbaugh, C.C. "DTPA therapy: The U.S. experience 1958-1987," in: *The Medical Basis of Radiation Accident Preparedness,* 2nd ed.*,*

2. Ricks, R. and Fry, S.A. eds., Elsevier Science Publishing Co., Inc., pp. 397-406, 1990.

3. Breitenstein, B.D., "1976 Hanford americium exposure incident: Medical management and chelation therapy." *Health Physics* 45(4): 855-866, 1983. Breitenstein, B.D., and Palmer, H.E. "Lifetime followup of the 1976 americium accident victim." *Radiation Protection Dosimetry* 26:317-322, 1989.

4. Bruenger, F.W., Taylor, D.M., Taylor, G.N., and Lloyd, R.D. "Effectiveness of DTPA treatments following the injection of particulate plutonium." *Int J Radiat Biol.* 60(5): 803-818, 1991.

5. Morin M., Nenot, J.C., and Lafuma, J., "The behavior of 237-Np in the rat." *Health Physics* 24:311-315, 1973.

6. Taylor, G.N., Mays, C.W., "Fetal injury induced by Ca-DTPA in dogs." *Health Physics* 35:858-860, 1978.

7. Mays, C.W., et al., "Zn-DTPA safety in the mouse fetus." *Health Physics* 36:526-529, 1979.

8. Kalkwarf, D.R., Thomas, V.W., Nielson, K.K, Mauch, M.L. "1976 Hanford americium exposure incident: Urinary excretion of trace metals during DTPA treatments." *Health Physics* 45(4): 937-947, 1983.

Radiogardase®-Cs

Insoluble Prussian Blue (ferric hexacyanoferrate, $Fe_4[Fe(CN)_6]_3$)

INFORMATIONAL MATERIAL

PACKAGE INSERT*

DESCRIPTION

IND 51,700, insoluble Prussian Blue, is to be used in the U.S. as a decorporation agent for patients internally contaminated with medically significant amounts of cesium and thallium. In this document, the name Insoluble Prussian Blue (PB) without further specification indicates the following compound:[1]

Ferric(III) hexacyanoferrate(II) "insoluble PB"
$Fe_4 [Fe (CN)_6]_3$
Molecular weight: 859.3
Color Index No. 77.510
CAS Registry No. 14038-43-8

Prussian Blue is distributed by Oak Ridge Institute for Science and Education (ORISE). ORISE is managed by Oak Ridge Associated Universities (ORAU), under contract with the U.S. Department of Energy (DOE), Contract No. DE-AC05-76OR00033. A selected bibliography of the world use of Prussian Blue in cesium and thallium decorporation therapy is given in the accompanying references.

INTRODUCTION

Insoluble Prussian Blue (PB), ferric hexacyanoferrate, $Fe_4[Fe(CN)_6]_3$ is a drug that enhances excretion of isotopes of cesium and thallium from the body by means of ion exchange. It has had a long and successful history in the treatment of internal contamination with radiocesium. Prussian Blue is currently only supplied by a German company, HEYL Chemisch-pharmazeutische Fabrik GmbH & Co. KG (HEYL GmbH), under the trade name Radiogardase®. The Oak Ridge Institute for Science and Education (ORISE) undertaking for this IND will: (1) make Insoluble Prussian Blue more widely available at Department of Energy (DOE) facilities for physicians to treat individuals with significant radiocesium and radiothallium contamination and (2) quantitate efficacy and establish a drug profile based on wider experience. In the DOE system, internal contamination with radiocesium is expected to be much more important than with thallium. This protocol will therefore deal primarily with decorporation therapy with PB for internal contamination with radiocesium.

Of the various radioisotopes of cesium, ^{137}Cs is the most important. ^{137}Cs is a common fission by-product material, a frequent active component of sealed sources, and an important radionuclide in radiation oncology. The use of ^{137}Cs falls under the jurisdiction of the Nuclear Regulatory Commission (NRC). It is a ubiquitous radionuclide found throughout the DOE system and in hospitals performing either gynecological brachytherapy or interstitial therapy for solid tumors. Until the Goiânia incident in Brazil,[2] there were very few cases of radiocesium contamination requiring decorporation therapy. However, there is an increasing potential for such contamination to occur and a need for specific therapy. The recent increase in workers performing remediation work at hazardous waste sites also requires that clinicians have Insoluble Prussian Blue available and understand the nature of its pharmacodynamics.

Insoluble Prussian Blue has been recommended for years as the drug of choice by national and international radiation protection societies for use in treating internal contamination with radiocesium. It was effectively used in the treatment of patients contaminated with ^{137}Cs in the 1987 Goiânia, Brazil accident under temporary clearance by FDA for "compassionate use" by the Oak Ridge Associated Universities' Radiation Emergency Assistance Center/Training Site (REAC/TS) program. The majority of the Prussian Blue used for treatment in the Goiânia, Brazil accident was supplied by HEYL GmbH.

**Reviewed and approved by the ORAU/ORNL Institutional Review Board for 12 months, December 1, 1999.*

CLINICAL PHARMACOLOGY

Insoluble Prussian Blue has a very high affinity for cesium and thallium, whose metabolism follows an entero-enteric cycle. These ions are ordinarily excreted into the intestine and reabsorbed from the gut into the bile, and then excreted again into the GI tract. Orally administered PB traps thallium or cesium in the gut, interrupts its reabsorption from the gastrointestinal tract and thereby increases fecal excretion. Thus, the biological half-life of thallium and cesium is significantly reduced after decorporation therapy with PB. PB itself is not absorbed across the gut wall in significant amounts.

The mechanism of cesium and thallium adsorption by hexacyanoferrates is not yet known in full detail. All authors discuss chemical ion-exchange as a mode of action, in which nonstoichiometric and stoichiometric cations of the drug are exchanged by thallium or cesium ions.[3] Physical adsorption on the large molecular surface, possibly interacting with water, may also be involved. This phenomenon would explain the influence of the drying procedure on the efficacy of the drug.
Inversion of the concentration gradient of toxic metals between the central compartment and target organs occurs commonly in decorporation therapy with chelating agents, but this has not been seen with PB. The effect of PB in experimental thallium and cesium poisoning has been investigated in various animal studies that are outlined below in detail.

Cesium

In-vitro studies have shown that cesium readily binds to PB and the cesium absorption capacity of various hexacyanoferrates does not differ significantly. Administration of a single dose of radiocesium and the concomitant oral application of PB results in reduction of cesium uptake from the gastrointestinal tract. In piglets, PB reduced ^{137}Cs uptake by more than 97%. Diminution of a ^{137}Cs-body-burden also depends on the dose of administered hexacyanoferrate (II) and if given as late as 60 minutes after ^{137}Cs administration, the enteral ^{137}Cs absorption is also suppressed. Autoradiography of rats administered labeled PB shows that the radioactivity is limited to the gastrointestinal tract.[4] In addition, chronic feeding of rats and piglets with ^{137}Cs-contaminated food and concomitant administration of PB resulted in reduced whole-body retention of ^{137}Cs.[5] In rats the effect on the whole-body retention was age-dependent. In younger animals, whole body retention was noted to be lower than in older animals, primarily due to a higher basal metabolic rate. In most cases where PB was given, the administered ^{137}Cs was found to be excreted primarily in the feces. In a mixture with other substances occasionally used in radiation medicine (for example Ca-alginate, potassium iodide), PB also decreased absorption of cesium into the organism and reduced the whole-body retention.[6]

Insoluble Prussian Blue increases the cumulative excretion of incorporated radiocesium in feces whereas in untreated animals most cesium is excreted in the urine. In animals treated with PB, fecal excretion predominates, resulting in a decreased biological half-life. In rats, decorporation therapy with PB resulted in the effective biological half-life diminished by 50% (~11 days vs. ~6 days) and in dogs from 11 to 6.5 days.[7] These animal results parallel the human kinetic data noted in the radiological accident in Goiânia.

Thallium

The efficacy of PB for treatment of thallium poisoning has been described in various case reports.[8-10] In patients even with severe thallium poisoning, most cases published in the literature have had a favorable outcome. Only three deaths have been reported.[11,12] Two of these individuals ingested 2400 mg and 4000 mg of thallium, respectively (lethal dose approximately 1000 mg). One died after a second ingestion of thallium. However, the majority of patients with thallotoxicosis exhibit a good clinical response.

In the more severe cases of thallium intoxication, additional treatment for enhanced elimination is used. If ingestion had occurred within the preceding 48 hours, gastric lavage has been carried out in many cases. Hemodialysis and forced diuresis have also been used in many cases and hemoperfusion has been carried out in very severe cases. To increase the fecal excretion, laxatives (mannitol) were used and occasionally forced diarrhea was induced. The pharmacology of PB with regard to thallium poisoning is expected to be similar to that for cesium.

Therapy of thallium poisoning, similar to that for cesium, is primarily directed to prevention of absorption from the intestinal tract, interruption of enteric cycling, and elimination of the metal complexes from the body. In cases of severe thallium intoxication, additional types of elimination treatment may be necessary, such as:

- Induced emesis, followed by gastric intubation and lavage.
- Forced diuresis (8-12 1/24h) until urinary thallium excretion is less than 1 mg/24h.
- Charcoal hemoperfusion, which has been proven successful if used within 48 hours of thallium ingestion and, therefore, during the distribution phase.
- Hemodialysis has also been reported to be effective in thallium intoxication.

A survey of the literature[10] shows that forced diuresis and hemoperfusion with activated charcoal increases the total clearance of thallium and decreases its biological half-life, $t_{1/2}$,as follows:

- without treatment: $t_{1/2}$ 9.5 to 15 days
- PB only: $t_{1/2}$ 3.0 ± 0.7 days
- PB+forced diuresis: $t_{1/2}$ 2.0 ± 0.3 days
- PB+forced diuresis+hemoperfusion: $t_{1/2}$ 1.4 ± 0.3 days

PHARMACOKINETICS

PB is a non-resorbable compound acting only in the gastrointestinal tract. To study the degree of resorption of PB from the gastrointestinal tract, ^{39}Fe-labeled PB was administered to piglets.[13] Low amounts of iron were absorbed from PB. The whole-body retention was measured after 14 days (% of applied doses):

K ^{39}Fe $[Fe(CN)_6]$	1.47%	$^{39}Fe_4[Fe(CN)_6]_3$	1.34%
KFe $[^{39}Fe(CN)_6]$	0.2%	$Fe_4[^{39}Fe(CN)_6]_3$	0.15%

Nearly all of the applied dose was found in the feces. Application of KFe $[^{39}Fe(CN)_6]$ to rats resulted in 0.03% whole body retention (only in the gastrointestinal tract) and in traces of radioactivity in the urine (0.14%). The amount in blood and skeleton was below the detection limit. Ninety-nine percent of the applied dose was excreted in feces. After administration of K^{39} Fe $[Fe(CN)_6]$ to rats, traces of radioactivity were found in the skeleton (0.11%) and in the blood (0.046%). The differences in distribution of $KFe[^{39}Fe(CN)_6]$ and K^{39} Fe $[Fe(CN)_6]$ showed, that no PB is absorbed, but the different ions K^+, Fe^{3+} and $[Fe(CN)_6]^{4-}$ are metabolized instead. No evidence was obtained for decomposition of $[Fe(CN)_6]^{4-}$. Further studies on the decomposition of PB, especially with respect to the release of cyanide, are outlined in the toxicology section. Histopathological examination of different organs showed no deposits of PB after oral administration of insoluble PB.[14]

After intraperitoneal (IP) administration of $KFe[^{39}Fe(CN)_6]$ the substance is eliminated by the reticuloendothelial system. The first day 40.5% of the radioactivity was excreted by urine; the fecal content was very small. On the second day 42% was found in the feces, and only a trace in the urine. After 4 days the body retention was 4.5%, with the most retention in the liver. Intravenous (IV) application of $KFe[^{39}Fe(CN)_6]$ and $K^{59}Fe[Fe(CN)_6]$ resulted in an entirely different metabolic behavior in rats. From $K^{59}Fe[Fe(CN)_6]$ more than 50% of the radioactivity was excreted in the urine, but from $KFe[^{39}Fe(CN)_6]$ only 0.06% was excreted. The fecal excretion was low for both. The distribution of the radioactivity into the organs after application of $KFe(^{39}Fe(CN)_6]$ was similar to that after application of $K_4[^{39}Fe(CN)_6]$ and differed from $K^{59}Fe[Fe(CN)_6]$. Whereas the radioactivity of $K^{59}Fe[Fe(CN)_6]$ persisted in the liver for 8 days, the activity of $K^{59}Fe[Fe(CN)_6]$ varied from the liver to the blood.

TOXICITY

The LD_{50} has been shown to be 1.13 mg/g after I.P. administration of ferric(III) hexacyanoferrate(II) to rats[4]. No tissue response could be detected. For oral application, the LD_{50} is >10 g/kg. Results of skin tolerance testing and eye testing in rabbits were negative.

PB contains cyanide ions bound to iron. At extremely low pH in the absence of oxidizing agents, PB decomposes and, under these circumstances, cyanide can be released. Since oral administration of PB is indicated in the treatment of thallium poisoning and cesium incorporation, the possibility of cyanide release must be excluded.

Cyanide labeled with ^{14}C was incorporated into PB and used to study the possibility of cyanide release after PB administration.

1. $KFe[Fe(CN)_6]$ $K^+ + Fe^{3+} + [Fe(CN)_6]^{4-}$
   $Fe_4[Fe(CN)_6]_3$ $4\ Fe^{3+} + 3\ [Fe(CN)_6]^{4-}$

2. $[Fe(CN)_6]^{4-}$ $Fe^{2+} + 6\ CN^-$

3. CN $\underset{\text{metabolism}}{CO_2 + SCN^-}$

In-vitro, the release of cyanide is negligible.[15] Piglets were also administered ^{14}C-labeled ferric(III) hexacyanoferrate(II). No labeled $^{14}CO_2$ was detected in the expired air, thereby demonstrating that no significant amount of cyanide ions were released from PB in the body. The amount of incorporated cyanide ions is apparently extremely small or nil.

When PB was applied orally to rats for 12 weeks, no significant changes in increased body weight were found. Histopathological changes were not detectable in the organs including the gut. For chronic administration of PB to rats, the LD_{50} is > 1 g/kg.

Oral application of PB in food containing 1% PB over 120 days or over 60 days resulted in no change of body weight. Food consumption and body weight increase was unchanged during 10 days or 4 weeks. No significant difference of average fluid intake of rats was detected in rats during a 60-day period. The well-being and body weight of dogs in no way was affected by PB during 11 days. At autopsy no pathological changes were observed.

PREVIOUS HUMAN EXPERIENCE

Thallium

Most of the patients who were treated immediately after Tl-ingestion with PB and other therapeutic regimens developed no, or only minimal traces of thallium-induced neurological symptoms, although the thallium levels were high. Some patients in whom start of treatment was delayed also recovered uneventfully. However, recovery progressed slowly sometimes. In some patients with severe clinical signs of thallium intoxication, clinical symptoms were not fully reversible at the time of discharge. Neurological disturbances, namely in the legs, and alopecia constituted most of the remaining clinical symptoms.

Cesium

The effect of PB on Cs decorporation initially was investigated in volunteer studies. A dosing schedule of Insoluble Prussian Blue of 1g tid was shown to reduce the effective biological half life of cesium to one-third of its usual value.[7,16] The administration of 0.5 g tid , (before and concomitantly given with) ^{137}Cs had no prophylactic effect on body burden. Patients tolerated Insoluble Prussian Blue without adverse effects except for slight obstipation. When PB was administered in a daily dose of 2 g divided in 10 single doses for 10 days, the biological half-life of ^{137}Cs was reduced from 115 to about 40 days.

In four of six volunteers, PB was found to block almost completely Cs uptake from contaminated food. However, the preexisting Cs body burden was not substantially decreased. The effect of PB varied individually, but did not appear to be dose-dependent. No adverse effects were observed.

The PB treatment of 46 patients with incorporated ^{137}Cs after the radiological accident in Goiânia, Brazil in 1987, when 249 persons had been contaminated externally or internally with ^{137}Cs, is described in the IAEA Report. Patients ages 4 to 38 years were treated with Radiogardase®-Cs up to 150 days. Doses generally ranged from 1 to 10 g daily. In four adult cases, 20 g was administered daily in divided doses. Children were given 1-1.5 g daily in 2-3 divided doses. Insoluble Prussian Blue was found to significantly expedite cesium decorporation in these cases. Increasing the dose of PB generally resulted in higher radioactivity in the fecal samples while the systemic burden was reduced. In a few patients, constipation was observed that could be treated easily using laxatives.

In another incident, five persons had accidental intake of ^{137}Cs. The effective half-life of the cesium depended on the individual and ranged from 36 to 124 days. The half-life was shorter when the subject=s weight was lower or the person was younger. PB accelerated the decorporation of cesium reducing the average effective half-life from 39 to 16 days.

In the 1987 Goiânia, Brazil ^{137}Cs contamination accident, an upper therapeutic range of Insoluble Prussian Blue was tentatively established at approximately 10 g orally per day in three divided doses. Doses higher than 10 g per day resulted in an increased incidence of gastritis, constipation and diarrhea. At six months' follow up, some patients still complained of gastrointestinal symptoms and one eventually developed a duodenal ulcer. Most of these adverse effects were mitigated significantly with dietary modification and with laxatives. It is also not certain whether these symptoms were due to other concomitant stressors, Insoluble Prussian Blue therapy, or other therapy. Several reviews of the scientific literature on use of PB in radiation accidents have recently been published.[18-24]

WARNINGS AND PRECAUTIONS

Insoluble Prussian Blue is effective only if gastrointestinal motility is intact. When insoluble Prussian Blue is given with tetracycline, it may retard the absorption of the tetracycline. There are no known absolute contraindications to the usage of PB, when medically indicated for decorporation therapy.

Usage in Pregnancy - Pregnancy Category C –

Insoluble Prussian Blue has been studied in pregnant rats with experimental thallium poisoning. The Tl-content of the placenta, brain, and liver of fetuses was noted to be reduced by PB, and the survival rate of the pregnant rats was increased. Oral administration of insoluble PB also was found to shorten the residence time of ^{137}Cs in pregnant, and lactating rats. The deposition of ^{137}Cs in the embryos of nursing young animals was similarly reduced. The efficacy of therapy with PB has been shown to be time-dependent. Start of treatment immediately after ingestion is most successful. As PB is not absorbed from the GI tract, teratogenic effects or appearance in milk are not to be expected. Pregnant and lactating women are therefore not excluded from treatment with PB.

ADVERSE REACTIONS

High doses during treatment over a prolonged period may lead to slight obstipation.

OVERDOSAGE

Overdosage by PB has not been described.

DOSAGE AND ADMINISTRATION

Insoluble Prussian Blue is administered orally. Depending on the severity of thallium poisoning or cesium incorporation, PB may be given from 3 g to 20 g, daily in three divided doses. Typically, for decorporation therapy for internally deposited radiocesium, the initial dosage is one gram three times daily and the dosage may be increased for more severe cases. The higher dose regimen (> 10 g daily) usually is preferred in acute poisoning with thallium. In cases of acute thallium poisoning in which thallium is still present in the stomach or the upper part of the small intestine, an initial dose of at least 3 g should be given at once.

The capsules of Radiogardase® -Cs are to be swallowed whole with some liquid or dispersed in warm water and drunk as a solution; the solution may also be administered via stomach tube following gastric lavage. If clinical findings suggest that oral ingestion is impossible, administration of PB is recommended by way of a duodenal tube. The duration of treatment depends on thallium or cesium identification in the stool by laboratory analysis.

HOW SUPPLIED

Insoluble Prussian Blue is supplied from HEYL GmbH in Germany as a 0.5 gram gelatin capsule for oral administration.

The Food and Drug Administration (FDA) requires that the Sponsor and Manager(s) of the IND be in a position to account for all ampules sent to investigator physicians. These physicians must, therefore, set up an accounting system on the supplies of Prussian Blue and be prepared to report their clinical experience annually, including observations on the safety and efficacy of the drug. The Manager(s) of the Prussian Blue IND will contact all co-investigators in June of each year to obtain this report. These observations will be incorporated into ORISE's summary report to the FDA for the preceding 12-month period.

SUMMARY OF ADMINISTRATION

To maximize efficacy, if the patient contaminated with ^{137}cesium or thallium also has been injured, assure that medical treatment is initiated as soon as possible. However, delay does not preclude the use of Prussian Blue (PB). The patient's respiratory/hemodynamic status should also be stable prior to administration of the drug. Since this application is directed to use of PB in the DOE facilities complex, the following guidelines pertain primarily to radiocesium since that isotope is expected, by far, to be the more commonly encountered isotope. The following guidelines are provided to facilitate rapid initiation of treatment.

Therapy Guidelines

A The internal burden of radiocesium should be ascertained after an accidental ingestion or inhalation by appropriate whole-body counting and/or by bioassay:

1. Determine the magnitude of the radiocesium accident. The appropriate annual limit of intake (ALI) should be determined with health physics assistance from 10 CFR20. For ^{137}Cs, this corresponds to 100 μCi for ingestion (3.7 E06 Bq) or 200 μCi (7.4 E06 Bq) for inhalation. For other radioisotopes of Cesium, the appropriate ALI should be determined.

2. An estimate of the magnitude of the accident may be determined by whole body counting, early stool or urine sampling, or by gastric lavage. Accidents in the DOE facilities complex are expected generally to involve either ^{137}Cs particulate inhalation or ^{137}Cs in a contaminated wound. In these cases, whole body counting or wound counting would be the preferred mode for initial determination of the magnitude of the accident.

3. After an initial whole body or wound count, the treating physician should propose a Prussian-Blue regimen based on the estimated body burden of ^{137}Cs.

4. The level of internal contamination should be categorized (e.g. low, intermediate, high). For initial treatment guidelines, we consider a low-level accident as 1-5 ALI, a moderate accident as 5-10 ALI, and a severe accident as greater than or equal to 10 ALI.

5. The appropriate daily dose of Prussian Blue should be based on the suspected level of internal contamination (e.g. low: 3 g daily; intermediate: 3-10 gm daily; high:10-20 g daily). All administration should be TID.

B In most cases requiring decorporation therapy, the extent of internal contamination is expected to be low to moderate (< 1-10 annual limits of intake, ALI). Prussian Blue decorporation therapy for radiocesium in these cases should be initiated at an initial dosage of one gram TID and titrated as necessary. In order to judge the efficacy of treatment, the patient should be followed periodically with both urine and fecal bioassay and with whole-body counting. In more serious cases of internal contamination with radiocesium, up to 10 grams or more of PB may be given daily in three divided doses. The patient should be warned that he/she may experience blue colored stool.

C It is expected in cases involving decorporation therapy that daily whole body counting and collection of 24 hour urine and fecal bioassay samples will be performed. This will allow proper evaluation of ^{137}Cs elimination curves.

D Since PB can also bind Na and K ions with lesser affinity than for Cs, those patients with potential for electrolyte abnormalities and/or cardiac problems should have periodic serum electrolyte evaluations at the discretion of the treating physician. Blood samples should also be collected every 12 hours for the first 96 hours post-accident for serum chemistry, especially, iron, ferritin, and serum electrolytes as indicated. A CBC should be collected initially and as indicated clinically thereafter. Vital signs should also be included in a timetable.

E The attending physician should consider reducing the dose of Prussian Blue in parallel with the decreasing whole body burden of ^{137}Cs. A case report form (CRF) has been developed and co-investigators are expected to record cesium body burden and bioassay results at defined time intervals. It is also imperative that a description of measurement methods be included to facilitate analysis of data.

F Hemodialysis and other extracorporeal clearance techniques have recently been proposed to aid elimination of radiocesium and such techniques could be considered for adjunctive therapy in severe cases of internal contamination. In very severe cases involving internal contamination with radiocesium, the guidelines for thallium poisoning could also be employed.

G Therapy for thallium poisoning is similar to that for cesium, except that an initial loading dose of 3 gm orally should be used. In cases of severe thallium intoxication, additional types of elimination treatment may be necessary, such as:

- Induced emesis, followed by gastric intubation and lavage.
- Forced diuresis (8-12 1/24h) until urinary thallium excretion is less than 1 mg/24h.
- Charcoal hemoperfusion, which has been proven successful if used within 48 hours of thallium ingestion and, therefore, during the distribution phase.
- Hemodialysis has also been reported to be effective in thallium intoxication.

In more severe cases of thallium poisoning, up to 20 grams of PB may be given daily in three divided doses, depending on the severity of the patient's condition.

Questions regarding the use of Prussian Blue may be referred to one of the following co-principal investigators at the Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831-0117:

Ronald E. Goans, Ph.D., M.D.
Co-principal Investigator, Prussian Blue IND
(865) 576-4049
Robert C. Ricks, Ph.D.
Co-principal Investigator, Prussian Blue IND
(865) 576-3131
Ronald D. Townsend, Ph.D.
Sponsor, DTPA IND
(865) 576-3300

REFERENCES

1. Martindale. (1982). *The Extra Pharmacopoeia*, 28th edition. J.E.F.Reynolds (Ed.); London: The Pharmaceutical Press; p.1749
2. IAEA. (1988). *The Radiological Accident in Goiânia.* International Atomic Energy Agency, Vienna.
3. Buser, H.J., Schwarzenbach, D.. Petter, W., Ludi. A. (1977). "The crystal structure of prussian blue: $Fe_4[Fe(CN)_6-]_3$ xH_2O." *Inorg. Chem.* 16(11): 2704-2709.
4. Brenot, A., Rinaldi, R. (1967). "Toxicite et efficacite comparees de quatre ferrocyanures dans la decontamination du cesium radioactif 134 (Comparative toxicity and effectiveness of 4 ferrocyanides in decontamination from radioactive cesium-134)." *Pathol. Biol.* (Paris). 15(1): 55-59.
5. Danetskaia, E.V., Lavrentev, L.N., Zapolskaia, N.A., Teplykh, L.A. (1977). "Otsenka zashchitnogo deistviia berlinskoi fazuri, al'ginata natriia i kal'tsiia fosfornokislogo po vykhodu opukholei Pri odnokratnom : khronicheskom deistvii smesi strontsiia-90 i (Evaluation of the protective effect of Prussian blue, sodium alginate and calcium phosphate according to tumor development after single and chronic exposure to strontium 90 and cesium 137 mixture)." *Vopr. Onkol.* 23(6): 57-61.
6. Kostial, K., Vnucec, M., Tominac, C., Simonovic, I. (1980). "A method for a simultaneous decrease of strontium, cesium and iodine retention after oral exposure in rats." *Int. J. Radiat. Biol.* 37(3): 347-350.
7. Richmond, C.R. (1983). "Accelerating the turnover of internally deposited radiocesium." In: *Diagnosis and Treatment of Deposited Radionuclides*; H.A.Kornberg, W.D.Norwood (Eds.); Amsterdam: Excerpta Mecia Foundation, 315-327.
8. Barbier. F. (1974). Letter: Treatment of thallium poisoning.; *Lancet* 2(7886): 965.
9. De-Groot, G., Van-Heijst, A.N., Van-Kesteren, R.G., Maes, R.A. (1985). "An evaluation of the efficacy of charcoal hemoperfusion in the treatment of three cases of acute thallium poisoning." *Arch. Toxicol.* 57(1): 61-66.
10. De-Groot, G., van-Heijst, A.N. (1988). "Toxicokinetic aspects of thallium poisoning. Methods of treatment by toxin elimination." *Sci. Total. Environ.* 71(3): 411-418.

11. Nielsen. J.S. (1974). "Akut thalliumforgiftning og behandling med berlinerblat.; (Acute thallium poisoning and treatment with Berlin-blue)." *Ugeskr. Laeger.* 136(52): 2930-2931.
12. Van-Kesteren, R.G., Rauws, A.G., De-Groot, G., Van-Heijst, A.N.P. (1980). "Thallium intoxication: An evaluation of therapy." *Intensivmed.* 17: 293-297.
13. Nielsen, P., Dresow, B., Fischer, R., Gabbe, E.E., Heinrich, H.C., Pfau, A.A. (1988). "Intestinal absorption of iron from ^{59}Fe-labeled hexacyanoferrates (II) in piglets." *Arzneimittelforschung*. 38(10):1469-1471.
14. Giese, W., Hantzsch, D. (1970). "Vergleichende Untersuchungen über die Cs-137-Eliminierung durch verschiedene Eisenhexacyanoferratkomplexe bei Ratten." *Zbl. Vet. Med.* 185-190.
15. Dvorak, P. (1970). "Hecacyanoferrate (II) als Thallium-Antidote. (Hexacyanoferrates (II) as thallium antidotes. Preparation and properties)." *Arzneimittelforschung.* 20(12): 1886-1888.
16. Strömme, A. (1983). "Increased excretion of 137-Cs in humans by prussian blue." In: *Diagnosis and Treatment of Deposited Radionuclides*. H.A.Kornberg, W.D.Norwood (Eds.); Excerpta Medical Foundation, Amsterdam; 329-332.
17. *NCRP Report No. 65, Management of Persons Accidentally Contaminated with Radionuclides*, National Council on Radiation Protection and Measurements, Bethesda, Maryland, 1979, pp. 77-79.
18. Korzun, V.N. (1991). "Decrease in internal irradiation from cesium radionuclides by using ferrocin (Prussian Blue)." *Med Radiol (Mosk)* 36(5): 23-27.
19. Farina, R., Brandao-Mello, C.E., Oliveira, A.R. (1991). "Medical Aspects of ^{137}Cs decorporation: the Goiânia radiological accident." *Health Physics* 60(1): 63-66.
20. Lipsztein, J.L., Bertelli, L., Oliveira, C.A., Dantas, B.M. (1991). "Studies of Cs retention in the human body related to body parameters and Prussian Blue administration." *Health Physics* 60(1): 57-61.
21. Lipsztein, J.L., Bertelli, L., Melo, D.R., Azeredo, A.M., Juliao,L., Santos, M.S. (1991). "Application of in-vitro bioassay for ^{137}Cs during the emergency phase of the Goiânia accident." *Health Physics* 60(1): 43-49.

22. Brandao-Mello, C.E., Oliveiria, A.R., Valverde, N.J., Farina, R., Cordeiro, J.M. (1991). "Clinical and hematological aspects of ^{137}Cs: the Goiânia radiation accident." *Health Physics* 60(1): 31-39.
23. Pearce, J. (1994). "Studies of any toxicological effects of Prussian blue in mammals - a review." *Food Chem Toxicol* 32(6): 577-582.
24. Melo, D.R., Lipsztein, J.L., de Oliveira, C.A., Bertelli, L. (1994). "^{137}Cs internal contamination involving a Brazilian accident, and the efficacy of Prussian Blue treatment." *Health Physics* 66(3): 245-252.
25. Verzijl, J.M., Wierckx, F.C., van Dijk, A., Savelkoul, T.J., Glerum J.H. (1995). "Hemodialysis as a potential method for the decontamination of persons exposed to radiocesium." *Health Physics* 69(4): 543-548.
26. Verzijl, J.M., Wierckx, F.C., Hennen, L.A., van Dijk, A., Glerum J.H. (1995). "The influence of extracorporeal clearance on elimination of radiocesium after internal contamination." *Health Physics* 69(4): 521-529.

See Parts 1 and 2 for

Sections 1 & 2 and Appendices