National stockpiles for radiological and nuclear emergencies: policy advice
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Foreword

An integral part of the World Health Organization’s work on health emergencies and on environmental health is the provision of policy advice and of assistance to Member States in strengthening their national capacity for preparedness, response and recovery after emergencies. This work contributes to implementation of the International Health Regulations (2005) (IHR) and to achievement of one of the ambitious goals set in the Organization’s Thirteenth Thirteenth Global Program of Work: to improve the health of three billion people by 2023.

As of May 2022, almost half of WHO’s Member States reported that they still lacked essential elements of preparedness for radiation emergencies as part of annual reporting to WHO on the state of core national capacities under the IHR. Essential elements of the public health response to health emergencies include national capability to identify and assess risk, to provide emergency health services and to maintain functional health facilities (e.g., ambulances, hospitals, laboratories, pharmacies), a qualified workforce and sufficient quantities of the necessary medical supplies and devices.

The COVID-19 pandemic and other health emergencies and humanitarian crises have highlighted the need to ensure access to medical supplies and devices for timely, efficient case management (both diagnosis and treatment) of diseases. This can be addressed by establishing national stockpiles of essential medicines and medical devices or through appropriate alternative arrangements for accessing such supplies through agreements with manufacturers or neighbouring countries.

This document describes protocols and practices for ensuring the essential elements of a national stockpile of medical countermeasures for radiation emergencies, particularly of the pharmaceuticals required to treat radiation injuries. It also addresses governance and management of such stockpiles. It supersedes the 2007 WHO report on development of stockpiles for radiation emergencies. It includes updated information on the pharmaceutical elements of stockpiles and additional information on medicines recently approved for clinical management of radiation injuries in several countries.

This publication was produced through the collaboration of a global network of experts and partners. We would like to thank them all for their support to WHO’s mission, thereby helping to increase global preparedness for radiological and nuclear emergencies.
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Preparation of the publication was coordinated and supervised by Dr Zhanat Carr, Radiation and Health Unit, Department of Environment, Climate Change and Health, World Health Organization, Geneva, Switzerland.

**Working group members**

Makoto Akashi, Tokyo Healthcare University, Japan;  
Marc Benderitter, Ind institut de Radioprotection et de Sûreté Nucléaire, France  
Andrei Bushmanov, Burnasayan Federal Medical Biophysical Center, Russian Federation  
Nicholas Dainiak, Yale University School of Medicine, United States of America (USA) (Co-Chair)  
Andrea DiCarlo-Cohen, National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA  
Ioana Ghiga, World Health Organization (contributed to the first meeting of the Working Group)  
Cornelius Hermann, Institut für Radiobiologie der Bundeswehr, Germany  
Atsushi Kumagai, National Institutes for Quantum Science and Technology, Japan  
Chunsheng Li, Health Canada, Canada (Co-Chair)  
Matthias Port, Institut für Radiobiologie der Bundeswehr, Germany

**Technical reviewers**

Brian Ahier, Health Canada, Canada  
Sergei Aleksanin, Nikiforov Russian Center of Emergency and Radiation Medicine, Russian Federation  
Bernadette Capello, World Health Organization  
Davi Christ Fassano Cesar, Eletronuclear Medical Assistance Foundation, Brazil  
Marc Desrosiers, Health Canada, Canada;  
Paul Eagan, Department of National Defence, Canada  
Nick Gent, United Kingdom Health Security Agency, United Kingdom  
Benedikt Huttner, World Health Organization  
Misa Imaizumi, Radiation Effects Research Foundation, Japan  
Siegfried Joussineau, Karolinska University Hospital and Karolinska Institutet, Sweden  
Mazen Malkawi, World Health Organization  
Bradley Mitchelmore, Public Health Agency of Canada, Canada  
Lorenzo Moja, World Health Organization  
Eun Kyung Paik, Korea Institute of Radiological and Medical Sciences, Republic of Korea  
Alegria Montoro Pastor, Hospital Universitario y Politécnico la Fe, Spain  
Maria del Rosario Perez, Argentina  
Mohamed Rbai, Morocco  
Christoph Reiners, University of Würzburg, Germany  
Urs Schanz, University Hospital Zürich, Switzerland  
Alla Shapiro, USA  
Leif Stenke, Karolinska University Hospital and Karolinska Institutet, Sweden  
Emilie van Deventer, World Health Organization  
Robert Whitcomb, USA

**Declarations of interest**

All members of the working group declared their interests according to WHO standard procedures. None of the interests declared was found to be significant.
Abbreviations and acronyms

ARS    acute radiation syndrome
ASCO   American Society of Clinical Oncology
CBC    complete blood count
CSF    colony-stimulating factors
DTPA   diethylenetriaminepentaacetic acid
EML    Essential Medicines List
FDA    (US) Food and Drug Administration
IAEA   International Atomic Energy Agency
IND    improvised nuclear device
IHR    International Health Regulations
LET    linear energy transfer
NPP    nuclear power plant
MCM    medical countermeasures
MSCT   mesenchymal stem cell therapy
PEG    pegylated
RDD    radiological dispersion device (“dirty bomb”)
RED    radiological exposure device
REMPAN Radiation Emergency Medical Preparedness and Assistance Network
SCT    stem cell therapy
WHA    World Health Assembly
WHO    World Health Organization
Glossary

**Acute radiation syndrome**
Sometimes known as radiation toxicity or radiation sickness, an acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short time (usually minutes). The major cause of this syndrome is depletion of immature parenchymal stem cells in specific tissues.

**Chelating agent**
See “Decorporation therapy”.

**Cytokine**
“Immunomodulating agents”, or agents that modulate or alter the immune system response and in the case of hematopoietic cytokines, promote the differentiation and growth of hematopoietic cells, resulting in increases in the number of white blood cells, red blood cells and platelets. Cytokines are small, soluble and plasma-membrane associated cell signaling molecules that facilitate cell-to-cell communication among immune and non-immune cells, and stimulate the movement of cells towards sites of inflammation, infection, and trauma.

**Colony-stimulating factors (CSF)**
Typically, CSFs are glycoproteins that control the production and even some functions of granulocytes and macrophages, the immune cells that are primarily responsible for protecting the body against infections. Although normally produced endogenously, they can be used as a drug if injected.

**Decorporation therapy**
Used to remove radionuclides from a body and thus to reduce the health risks due to their intake. Includes reduction and/or inhibition of absorption from the gastrointestinal tract, isotopic dilution and use of diuretics, adsorbents and chelating agents to expedite elimination from the body.

**Determination effects**
See “Tissue reactions”.

**Dose, radiation**
A measure of the energy deposited by radiation in a target.

- **Absorbed dose**: the fundamental dosimetric quantity. The energy imparted by ionizing radiation to a suitably small volume of matter divided by the mass of that volume. The unit is Gray (Gy). 1 Gy = 1 joule per kilogram.
- **Effective dose**: a measure of dose designed to reflect the amount of radiation detriment likely to result from the dose. The unit is Sievert (Sv).

**Doximetry**
Estimation and evaluation of radiation effects by measuring and/or calculating radiation dose from the external or internal exposure by using physical and biological methods, clinical assessments, as well as modeling and calculations.

**Dosage (of a medicine)**
Schedule for administration of a pharmaceutical compound in a prescribed amount.
Emergency, radiation
A non-routine situation or event that necessitates prompt action, primarily to mitigate a hazard or adverse consequences for human life, health, property or the environment. Includes (i) nuclear and radiological emergencies; and (ii) situations for which prompt action is warranted to mitigate the effects of a perceived radio-nuclear hazard.

- **nuclear emergency**: an emergency involving exposure to ionizing radiation resulting from a nuclear chain reaction or from the decay of the products of a chain reaction (e.g., nuclear power plant (NPP) reactor core melt-down, or a nuclear detonation)
- **radiological emergency**: an emergency involving exposure to ionizing radiation, either accidental or deliberate, not resulting from a nuclear chain reaction, nor the decay of the products of a chain reaction (e.g., lost radioactive source, transport accident or over-exposure in a medical, research or industrial facility as a result of inappropriate use of radioactive sources or exposure generating devices).

In this document, for the sake of brevity, the term radiological and nuclear emergency is at times is replaced by radiation emergency, which encompasses both types, regardless of the origin and scenario.

Formulation (pharmaceutical)
The composition, in both galenic and chemical forms, and dosage of a pharmaceutical product (e.g., the exact quantity of potassium iodide in milligrams in a tablet).

Exposure (to radiation)
The act or condition of being subject to irradiation. Can be either external (due to a source outside the body), or internal (due to a source within the body). Can be acute or chronic.

Exposure pathway
A route by which radiation or radionuclides can reach humans and cause exposure. It may be a simple, e.g., external exposure to airborne radionuclides, or a more complex chain, e.g., internal exposure from drinking milk from cows that ate grass contaminated with deposited radionuclides.

Half-life (of a radionuclide)
The time required for the activity in a radionuclide to decrease by half due to a radioactive decay process.

- **Biological half-life**: is the time taken to reduce by half the amount of a radionuclide in a specified tissue, organ or part of the body as a result of biological elimination processes. Can be accelerated by decorporation therapy to reduce the duration and dose of the internal exposure.

Intake (of a radionuclide)
The act or process of taking a radionuclide into the body by inhalation, ingestion, wound contamination or skin absorption in a given time or as the result of a given event. Intake can be acute or chronic.

Internal exposure
Exposure resulting from radionuclide intake into the body by inhalation, ingestion, wound contamination or skin absorption. Radionuclides irradiate tissues where they are located until the radioactive material is fully decayed over time and is no longer radioactive or is removed by the body either naturally (by urinary or fecal excretion), or by decorporation therapy. Note that not all internal contamination can be removed by the body without intervention.

Iodine thyroid blocking
An urgent protective action involving administration of stable iodine (typically KI tablets) in a radiological emergency or nuclear accident under the following conditions: (a) if exposure due to radioactive iodine is involved, (b) before or shortly after release of radioactive iodine and (c) within only a short time before or after intake of radioactive iodine.

Ionizing radiation
Radiation capable of producing ion pairs in biological materials. Examples of ionizing radiation are alpha and beta particles, gamma rays, X-rays and neutrons. Examples of non-ionizing radiation are electric and magnetic fields, radio waves, microwaves and optical radiation.
Isotope (see also Radionuclide)

Nuclide with the same number of protons (thus the chemical element) but different numbers of neutrons. Isotopes can be stable (non-radioactive) or non-stable (radioactive) For example, Cs has 40 known isotopes, including Cs-133 which is stable, while the others are radioactive.

Local (cutaneous) radiation injury

Injury to the skin and underlying soft tissue, muscles and bone from an acute localized high-dose external radiation dose is referred to as cutaneous radiation injury or local radiation injury.

Mass casualty event

Any health emergency event resulting in number of victims large enough to disrupt the normal course of emergency and health services.

On/Off label use (of a medicine)

In “on-label” use a drug is used for the same indication, dose, route of administration, patient populations and drug formulation for which it was originally approved, whereas “off-label” is the use of an approved drug for a different medical condition that is not the same as that for which it was approved.

Radioactivity

The property of an unstable atomic nucleus to lose energy by emitting radiation (radioactive decay). Radioactivity also refers to the number of radioactive decays occurring in a given quantity of material per unit time. The SI unit of radioactivity is becquerel (Bq), or radioactive decay per second.

Radionuclide

Also called radioactive isotope or radioisotope. An unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. Radionuclides may occur in nature, be made in a laboratory for research or medical purposes or be released in the environment as a result of a radiological or nuclear emergency.

Stem cell

Stem cells include pluripotent cells, which can develop into many different types of cells in the body and serve as a repair system for the body. There are two main types of stem cells: embryonic stem cells (exist only at the early stage of development) and adult tissue-specific stem cells. Stem cells are different from other cells in the body in three ways: (i) they can renew themselves; (ii) they are nonspecialized and cannot carry out specific functions of their progeny; and (iii) they can differentiate, i.e., become specialized cells. Haematopoietic stem cells in bone marrow give rise to haematopoietic lineage cells. Mesenchymal stem cells give rise to bone, adipose and cartilage tissue.

Stochastic effect

A radiation-induced health effect resulting from damage in a single cell, such as cancer and heritable effects. The frequency of the event, but not its severity, increases with an increase in the dose. For protection purposes, it is assumed that there is no threshold dose. Examples of stochastic effects are solid cancers and leukaemia.
Tissue reactions (deterministic effects of radiation)
Injury of tissues and organs due to cell death. Beyond certain thresholds, radiation can impair the functioning of tissues and/or organs and can produce acute effects such as skin redness, hair loss, radiation burns or acute radiation syndrome (ARS). These effects are more severe at higher doses and higher dose rates. For instance, the dose threshold for acute radiation syndrome is about 1 Sv (1000 mSv). Early tissue effects of radiation exposure occur in turnover tissues, where proliferative impairment results in hypoplasia. Late tissue reactions, based on combined parenchymal, vascular and connective tissue changes, result in loss of function in the exposed volume; consequential late effects develop through interactions between early and late effects in the same organ; and very late effects are dominated by vascular sequelae. In some cases, deterministic effects are modifiable by post-irradiation procedures, including biological response modifiers.

Urgent protective action
A protective activity in the event of an emergency which must be taken promptly (usually within hours) in order to be effective and the effectiveness of which will be markedly reduced if it is delayed. The most commonly considered urgent protective actions in a nuclear or radiological emergency are sheltering in place, iodine thyroid blocking, evacuation and decontamination of individuals. These are followed by early protective actions, which can be implemented in the first few days, e.g., restriction of the consumption of potentially contaminated food.

Whole body counter
Device that measures the ionizing radiation (typically gamma rays) emitted from the inside of body and provide an estimate of the radioactivity present in the body due to intake of radionuclides (resulting from an emergency or planned intake for medical purposes).

Whole body exposure (total body exposure)
Uniform irradiation of all organs and tissues of the human body. The term is used in dose assessment.
The International Health Regulations (2005) require all countries to establish national capacity and secure resources for responding to health emergencies; however, preparedness for radiation emergencies is consistently reported as the weakest area of preparedness in many countries. In 2021, the Seventy-fourth World Health Assembly called for building the required capacity, capability and resources, including establishment of national stockpiles of the drugs and supplies necessary for managing human exposure to radiation or ensuring that such stockpiles could be accessed elsewhere.

The process of establishing a national radiation emergency stockpile starts from mapping the most likely scenarios. A radiological emergency or nuclear accident may occur at a nuclear power plant or a fuel cycle facility; at a medical or research facility or in an industrial setting in which radiation sources are used or radioactive materials are processed; during transport of radioactive materials. Radiation may also be used maliciously to attack individuals or a society. The basic principles and approaches for setting up a stockpile are, however, similar. The size and the formulary of a stockpile depend on the emergency response concept of operations, estimated from reliable data for national risk profiles, the size of the populations that would be affected by specific scenarios and the available resources and capabilities of the health systems of the country.

In addition to generic medical supplies required for any health emergency, specific medical products are required for managing radiation injuries. The formulations of the products should be amenable for use in mass casualties, with minimal medical oversight. As storage is necessary, products that have minimal refrigeration requirements and long shelf-lives are preferred. Any health emergency requires stockpiling of elements that are common to several threats, and it is important to ensure the availability of other products stockpiles which could be rapidly repurposed for a radiation emergency.

Clinical evidence about the use of blocking and decorporating agents, as well as cytokines is limited. Only a few agents have proven to be effective for treating radiation injuries and internal radionuclide contamination, based on experience from past accidents. When no WHO guideline was available for the drug to be included in the stockpile formulary, the overall process for decision-making was based on consensus of the WG experts and the outcome of the peer-review process.

Internal exposure to radionuclides, if their uptake is not blocked or the nuclide is not removed from the body, could lead to immediate and long-term health consequences. Decorporation (removal from the body) and blocking agents can reduce the body burden of these contaminants e.g.: stable iodine is administered to prevent or reduce the exposure of the thyroid to radioactive iodine; Prussian blue is applied to remove radioactive cesium from the body; and calcium or zinc diethylenetriaminepentaacetic acid (Ca/Zn DTPA) is used for treatment of internal contamination with transuranium radionuclides. These and other elements of such stockpiles should be made rapidly available in case of radiation emergencies.
One of the most serious outcomes of over-exposure to radiation is acute radiation syndrome (ARS), which manifests as a haematopoietic syndrome and, depending on the severity of the exposure may further progress as gastrointestinal, cardiovascular and neurological syndromes. This document addresses only treatment of haematopoietic and gastrointestinal syndromes, as cardiovascular and neurological syndromes are considered non-salvageable and require only palliative care. Certain pharmaceutical products used to treat other clinical conditions have been approved for ARS management in some countries. Products of choice for management of haematopoietic syndrome include cytokines - growth factors that enhance proliferation of progenitor blood cells, facilitate myeloid maturation, protect against programmed cell death and enhance cell function. Erythropoietin, a growth factor currently used in clinical management of anaemia, is also administered to mitigate radiation-induced anaemia and reduce the need for blood transfusion. Agents for management of gastrointestinal injury, in addition to replacement of fluids and electrolytes, include antiemetic compounds and anti-diarrhoeal drugs; antimicrobials, antibiotics and anti-fungal and anti-viral agents are given for management of infections related to ARS. In most reported scenarios of exposure to radiation, haematopoietic and gastrointestinal tract injuries are responsible for early deaths. People who either survive ARS or receive sublethal exposure might then be susceptible to late tissue damage, referred to as the “delayed effects of acute radiation exposure”, and some products to address late outcomes are being currently studied.

Maintenance of a stockpile requires continual monitoring and evaluation, and the formulary must be regularly reviewed and updated to reflect state-of-the-art management and advances in logistics, transport and storage. Quality assurance and quality control measures must be applied continually to maintain the currency, accuracy and completeness of the stockpile. A protocol for a stockpile and decision-making should include criteria for triage and setting priorities for allocation and distribution in cases of limited availability of medical products. Governance and management of a radiation stockpile are based on assumptions about the types of radiological incidents anticipated. A variety of specialist skills are necessary to establish a radiation stockpile, including health-care providers trained in radiation medicine and/or emergency medicine, laboratory specialists, pharmacists, emergency response coordinators, logisticians and communications experts. Biomedical engineers will be required to maintain and calibrate equipment. Regular training should be provided to develop and update the skills of all personnel in conducting emergency operations. A communications strategy is also necessary in management of a stockpile, such as for explanation of timelines and priorities for access to certain products, should there be limited quantities.

National health authorities, health-care facilities, pharmaceutical suppliers and logistics, civil defence and emergency services each have specific responsibilities with regard to the multiple aspects of stockpiles development, maintenance and usage. These include developing appropriate national legislation, setting up the financing and acquisition routes, arrangements for maintenance, storage, transport, deployment, replenishment of stockpiles, as well as monitoring and evaluation of their use. Coordination among local, regional and national emergency response stakeholders and stockpile managers is essential to ensure that stockpiles are functional and rapidly accessible in an emergency. When resources are limited, arrangements can be put in place to share national stockpiles between countries, especially for those with a low risk of radiation emergencies.
A concept of operations, elaborated collaboratively by all stakeholders involved in emergency response, is vital for managing a stockpile. It describes the overall strategy and goals of its use, conditions under which the stockpile would be used, and how the stockpile is managed and maintained. In addition, it defines the formulary and size of the stockpile according to operational assumptions, provisions for purchase and contract management, as well as the location and facilities for the stockpile storage. It should provide details of inventory management, emergency protocols, staffing requirements and integration of the stockpile into overall local, regional and international emergency response plans.

Establishing a national stockpile incurs a substantial initial cost, and maintaining it requires reliable, sustainable sources of pharmaceuticals, supplies and equipment and committed financial and human resources. Various approaches have been used for stockpile management and access. The inventory may be physical, whereby products are purchased, stored in warehouses and removed from the stockpile when they expire, whereas a vendor-managed inventory allows a product to be stored on the vendor’s site, where products are routinely rotated to avoid expiration. A virtual stockpile is an agreed quantity of a medical product set aside by manufacturers or vendors for emergency allocation.

The publication takes a look at the role of the national health authorities in stockpiles development vis-a-vis the role of WHO. As the leading international organization in public health with both the authority and responsibility to assist in health emergencies, WHO provides advice and guidance to countries on public health preparedness and response to radiation emergencies, including stockpile development. In health emergencies WHO may assist in procuring or sharing medical supplies among countries.

Research is making progress in developing novel treatments and achieving technical advances that may result in new products for use during a radiation emergency. This report includes a brief review of selected emerging technologies and drug formulations, including potential repurposing of products previously approved for other indications.

In addition, the publication also provides examples of practices in establishing and managing a national stockpile in selected countries.
National stockpiles for radiological and nuclear emergencies: policy advice
1. Introduction

1.1 Background

The International Health Regulations (2005) (1) require all countries to establish national capacity and secure resources for responding to health emergencies. Preparedness for radiation emergencies is consistently reported as the weakest area of preparedness in many countries. In 2021, a resolution of the Seventy-fourth World Health Assembly stated that “further sustained efforts are still needed in the areas of chemical events, capacities at points of entry and radiation emergencies.” (2). The required capacity, capability and resources include establishment of a national stockpile of the drugs and supplies necessary for managing human overexposure to radiation or ensuring that arrangements are in place for accessing such stockpiles elsewhere.

Public health providers in all countries are required to provide medicines and supplies to their populations for use in public health emergencies. Whether it be a natural disaster, a man-made catastrophe, a pandemic, a terrorist attack or armed conflict, large quantities of medical supplies are required during an emergency that threatens human life. As the leading global health agency, the World Health Organization (WHO) facilitates access to such supplies and provides approaches for sharing stockpiles (3–5).

For radiation emergencies, WHO provides advice to public health specialists on the composition of a national stockpile of medical countermeasures (MCM), including medical supplies and equipment. This document describes existing protocols and practices for ensuring the essential elements of a national stockpile, particularly for the pharmaceuticals required for treatment of radiation injuries and addresses its governance and management. It supersedes a WHO report on stockpiles for radiation and chemical emergencies issued in 2007 (6). Since then, significant progress has been made in clinical management
of radiation injuries. Concepts and operations used in emergency, radiological and nuclear medicine have been cross-fertilized, and topics such as activation of an emergency plan, the principles of radiation safety, radiation detection, dose assessment, patient stabilization, medical triage, decontamination and specific MCM are now formally taught to health-care providers at all levels of their training and expertise. Coordination of local medical responses and resource utilization in regional, national and international plans for a radiological or nuclear incident is widely recognized as essential for a successful response. In addition to new MCM, experience in the management of recent radiation emergencies has increased understanding of patient needs and elucidated the potential of decorporation therapy (removal from the body) and of inclusion of psychosocial support for patients, responders and the general public (7–12). Furthermore, health emergencies such as the COVID-19 pandemic have provided new insight and understanding of complex public health responses, and countries throughout the world are conducting advance planning for health emergencies. A vital element of such plans is establishment of stockpiles of medical equipment, supplies and pharmaceuticals.

1.2 Scope

The document focuses on pharmaceutical products required for clinical management of radiation injuries resulting from external and/or internal overexposures to ionizing radiation. The document includes approaches to setting up and managing a national stockpile for radiological and nuclear emergencies and the roles of stakeholders and briefly outlines current research in the field of MCM. While generic MCM used in outbreaks and other health emergencies include biological products (e.g., vaccines, blood products and antibodies), drugs (e.g., antibiotics, antivirals, painkillers, and fluids) and devices (e.g., diagnostic tests to identify threatening agents and personal protective equipment), this document focuses on medicines and equipment for the diagnosis, prevention, or treatment of radiation injuries. Other medical supplies, such as devices for detecting and measuring radiation and personal protective equipment, are not covered.

1.3 Target audience

The main intended readership of this policy advice is public health administrators and public health professionals who are responsible for preparing for and responding to radiological and/or nuclear emergencies. This policy advice is also addressed to health-care providers involved in response to radiation emergencies.

1.4 Contributors to the advice

A working group (WG) of the WHO Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) was set up in 2021, which comprised experts and relevant stakeholders in multiple disciplines, including a guideline methodologist and experts in the field of radiation emergency medicine. The group provided input at all stages of the process and played the main role in development of policy advice. The group included experts from three of the six WHO regions and absence of conflicts of interest was ensured. The group was convened for five on-line meetings in 2021–2022 to develop this document.
1. Introduction

An external review group was composed of experts in relevant fields (such as radiation emergency medicine, toxicology, operational aspects of stockpiling) and selected technical programmes at WHO. The experts reviewed the draft document and commented on the technical accuracy, clarity of language and implications for implementation. The feedback was discussed by the working group and included in the draft.

1.5 Management of conflicts or interests

The disclosure and appropriate management of relevant financial and non-financial conflicts of interest of WG members and other external experts and contributors is a critical part of WHO publications. According to WHO regulations, all experts must declare their interests prior to participation in WHO processes and meetings. All WG members were therefore, required to complete a standard WHO declaration of interests form before developing policy advice. All the declarations were reviewed before the experts’ invitations to participate were issued on the criteria for assessing the severity of conflicts of interests. All findings from the declaration of interests forms received were managed in accordance with the relevant WHO rules on a case-by-case basis and communicated to the experts at the start of the first meeting.

1.6 Methodology for content development

The WG reviewed the WHO 2007 report, performed a literature review of scientific publications in PubMed and other databases and sought consensus statements from professional bodies and/or national health authorities (examples of national practices are provided in the annex). These sources were considered to define the size of the national stockpile according to emergency scenarios, the choice of clinical outcomes (e.g., ARS), the stockpile formularies and the advice on stockpile management.

Clinical evidence about the use of blocking and decorporating agents and cytokines is limited. Only a few agents have proven in past accidents to be effective for treating radiation injuries and internal radionuclide contamination. When no WHO guideline was available for the MCM to be included in the stockpile formulary, overall decision-making was based on consensus of the WG experts and the outcome of peer review.
In order for policy-makers to make decisions about establishing a national stockpile for radiation emergency response, they must be aware of the main factors and conditions that define the scope and elements of such a stockpile. This section provides brief information on radiation and its effects on human health (Box 1).

Depending on the severity of exposure to ionizing radiation, both external and internal exposure may lead to dose-dependent, predictable tissue reactions (also known as deterministic effects) or stochastic effects. Tissue reactions may be acute, subacute (occurring shortly after exposure) or delayed (developing months or years after exposure). Severe tissue reactions may include permanent injuries, such as tissue necrosis and death. Some of these reactions can be modified by post-irradiation therapy, including biological response modifiers such as cytokines and growth factors that stimulate differentiation and proliferation of progenitor or stem cells and vascular modifying agents that delay or prevent organ damage.

Systemic effects after exposure to a high dose and high dose rate of ionizing radiation (mostly from penetrating radiation such as X-, γ-rays, and neutrons) may result in acute radiation syndrome (ARS), also known as “radiation sickness”. ARS is defined as a spectrum of clinical signs and symptoms such as nausea, vomiting, diarrhoea, fever, headache, malaise, cognitive impairment and reduced production of blood cells (cytopenia) resulting characteristically from damage to the haematopoietic, gastrointestinal, cardiovascular and/or central nervous systems. Practical guidance for assessing and managing radiation injury is provided in the European Society for Blood and Marrow Transplantation pocket guide (14). ARS follows a dose-dependent clinical course that can be divided into prodromal, latent and manifest periods of illness (15). The intensity and length of these periods depend on the exposure dose, rate of dose delivery, radiation quality and other factors, such as coexisting trauma, thermal burns, pre-existing medical
conditions and susceptibility factors. Dose thresholds have been identified for each ARS subsyndrome, such as > 1 Gy for haematopoietic subsyndrome, > 6 Gy for gastrointestinal subsyndrome and > 8 Gy for neurovascular subsyndrome.

Box 1. Basic facts about radiation

Ionizing radiation is a type of energy released by unstable atoms that travels in the form of electromagnetic waves (γ- or X-rays) or particles (such as neutrons and α and β radiation). The spontaneous disintegration of atoms is called “radioactivity.” People are exposed daily to both natural and man-made sources of radiation throughout their lives. Natural exposure is due to inhalation and ingestion of the many naturally occurring radioactive materials in soil, water, and air.

Exposure may be internal or external (or a combination) through various pathways. People can be exposed to ionizing radiation, for example at home to natural background radiation, as a result of a planned intervention at a workplace (occupational exposure) or a medical facility or as a result of an accident or emergency.

Excessive exposure to radiation may damage living tissues and organs, depending on the amount of radiation received. The extent of damage depends on the type of radiation, the sensitivity of the affected tissues and organs, exposure pathway, the radioactive isotopes involved, individual characteristics of the exposed person (such as age, gender, and underlying conditions) and other factors.

The amount of radiation received is measured as the radiation dose. The risk of specific health effects depends on the dose. At very high doses, radiation can impair the functioning of tissues and/or organs and have acute effects, such as skin redness, hair loss, radiation burns, acute radiation syndrome or even death. The higher the dose, the more severe the biological effects. If the radiation dose is low or is delivered over a long period (low dose rate), the risk is substantially lower, as the damage to cells and molecules may be repaired by the body. At very low doses, such as those from natural sources, health effects such as cancer cannot be attributed to radiation because of the limitations of scientific measuring tools, and the likelihood of effects of this type is proportional to the radiation dose; they may never occur. The risk is higher for children and adolescents, as they are significantly more sensitive to radiation than adults.
Local radiation injury or cutaneous radiation syndrome (CRS) occurs when a body part (such as the skin or a limb) is exposed to ionizing radiation. CRS may occur alone or as part of injury throughout the body. Industrial high-dose radiation sources are a frequent source of accidents due to equipment maloperation or user error. Local doses of \( \geq 15 \text{ Gy} \) require special care, including dose assessment, dose-guided surgery and/or innovative treatment therapy such as administration of mesenchymal stem cells (16) (see section 6.1). This type of injury may also have delayed effects, resulting in fibrosis of soft tissue and other disorders, reducing the quality of life due to disability.

Stochastic effects are radiation-induced diseases or heritable effects. The probability of such an effect, but not its severity, is regarded as a function of dose, with no dose threshold. Thus, the probability of stochastic events increases as the radiation dose increases. Stochastic effects may be caused by mutations in somatic cells and include cancer in an exposed individual (17) or in offspring after birth due to exposure in utero.

Most people affected by a nuclear power plant accident would be exposed to low doses of radiation and mostly suffer mental health and psychosocial impacts, although some may develop stochastic effects. A national radiation emergency stockpile addresses mainly clinical management of deterministic effects. Other elements of the stockpile address reducing exposure and thus alleviating the risk of stochastic effects, such as prevention of thyroid cancer in people exposed to radioactive iodine at a young age.
3. National stockpiles: where to start?

Various factors have an impact on the decision to establish a national radiation emergency stockpile and the necessary composition and size to ensure a country’s preparedness for a radiological or nuclear emergency. The first step is risk mapping to determine the most likely emergency scenarios. A careful analysis of the country’s risk profile, geopolitical and demographic situation and available resources is required to justify planning a national radiation emergency stockpile. For example, a small island country might decide not to use the public health resources, which may be required for higher priorities, in order to prepare for a nuclear power plant (NPP) accident that would never occur.

3.1 Scenarios to be considered

A radiological or nuclear accident may occur at a NPP or a fuel cycle facility after a criticality event; radioactive materials may be released at a medical or research facility in which radiation sources or radioactive materials are used; accidents may occur at an industrial facility in which radiation is used for radiography, sterilization, well logging, or where radioactive waste is reprocessed; or in situations involving transport of radioactive materials.

During a criticality accident, such as that which occurred on 30 September 1999 in Tokai-Mura, Japan, people may be irradiated by a high flux of neutrons and γ-rays (18). During a severe accident at a nuclear facility, such as those that occurred on 26 April 1986 in Chernobyl, Ukraine (19), and on 11 March 2011 in Fukushima, Japan (12), significant amounts of radioactive material may be released into the environment,
where workers, first responders and the public may be exposed externally to radiation in the air or deposited on the ground and internally through ingestion of food and water contaminated with radionuclides such as radioactive iodines, isotopes of caesium and strontium and other fission and activation products such as the actinides.

As use of radiation in medicine is rapidly increasing, patients and health-care workers in nuclear medicine for medical imaging and therapy may be accidentally overexposed.

Industrial accidents may occur when radioisotope sources are mishandled or lost or when their containment, seal or shielding is damaged during their production, transport or use. If a source casing is ruptured, the radioactive material may be dispersed, resulting in contamination of equipment or of several individuals. Internal exposures may result from inhalation of radioactive material, inadvertent ingestion of radioactive material or contamination of a wound (20). Such accidents may result in significant doses of radiation. Most past serious radiation accidents involved only a single radionuclide, such as $^{60}$Co, $^{137}$Cs, $^{238}$Pu or $^{192}$Ir. A source in close proximity can cause significant external exposure to one or several individuals. The persons involved may be workers at the facility or members of the public.

Radiation may also be used maliciously to attack individuals or a society from a radiological dispersal device (RDD), a radiological exposure device (RED), or even an improvised nuclear device (IND). Furthermore, a deliberate attack may occur on a nuclear facility with a large inventory of radioactive materials, resulting in discharge of significant amounts of radioactive material into the environment.

An RDD may be used covertly or as a detonation to disperse a significant amount of radioactive material. Affected individuals may be contaminated externally by the debris or internally through inhalation, ingestion or contaminated wounds. Direct exposure can also occur from the remaining fragments and debris. Another example of covert dispersion is deliberate contamination of food or water supplies with a radioactive material in a targeted attack on a specific individual (21) or the public at large.

An RED device contains highly radioactive material designed to intentionally expose targeted individuals or the public. Examples include concealing an unshielded radioactive source in the workplace or vehicle of targeted individuals or in a place frequented by the public (such as an office building, shopping mall or cinema) or public transport.

An IND is a crude nuclear weapon of a yield that can vary widely, depending on its sophistication. At high yield, the extreme heat, powerful shockwaves and acute exposure may be lethal over a significant distance from the epicentre. Even deployment of a low yield improvised nuclear devices may scatter massive amounts of radioactive fission products and remaining fissile material into the environment (22). Use of nuclear weapons remains a serious threat within military conflicts and humanitarian crises placing the health and lives of civilians at risk.

Although exposure scenarios vary, the basic principles and approaches for establishing stockpiles for any of these scenarios is similar. Scenarios will not change the protocols for clinical management of radiation injuries. The national and regional risk profile, potential scenarios and the scale of a potential emergency define the scope and the size of the national stockpile.
3. National stockpiles: where to start?

3.2 Size of the stockpile

The size of a national stockpile depends on the concept of operations for its development and use (see section 5.3). The quantities of pharmaceutical agents and medical supplies are determined by (a) the anticipated number of casualties, (b) the distribution of injuries requiring urgent or long-term therapy, (c) the medication dosing schedule and (d) the anticipated duration of treatment. It may be difficult to make a realistic estimate of the number of victims requiring medical treatment, as the number of people involved in an incident does not necessarily reflect the number of patients requiring treatment. Furthermore, the density and activity of the population during a radiation incident affect the acuity of medical injuries and the magnitude of the medical response.

For example, the release of radioactive material from a low-yield (1 kT) nuclear detonation over a dense urban population may expose hundreds of thousands of individuals to a potentially high dose and/or dose rate of radiation. It may result in tens of thousands of victims requiring emergency treatment and hundreds of thousands requiring psychological and emotional support (Table 1). The estimates for a higher-yield (10 kT) device are increased by a factor or two or three. The type (or quality) of radiation released (high vs low linear energy transfer) also partly determines the anticipated need. Thus, it has been suggested that approximately 1% of people exposed to radioactive material released from an RDD or “dirty bomb” will require emergent or urgent medical treatment (23). In this case, the number of people requiring emergency treatment may be in the tens and the number of those requiring psychological or emotional support in the thousands or tens of thousands. In the case of exposure to radioactive material released during an NPP accident, millions of people may be exposed to low doses of radiation, as seen after the Chernobyl NPP accident in 1986 (24). In such a scenario, emergency protective actions such as sheltering and limiting consumption of contaminated food and water are more efficient in protecting health and reducing radiation risk. Therefore, the number of MCM and supplies required for a public health and medical response may vary from tens to hundreds of thousands (or possibly millions) of doses and treatments.

Table 1. Modelled mass casualty scenarios for 1 kT and 10 kT nuclear detonations

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Radiation dose (Gy)</th>
<th>1-kT detonation</th>
<th>10-kT detonation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined injuries (minimal to intensive care)</td>
<td>All doses</td>
<td>1000–3000</td>
<td>15 000–24 000</td>
</tr>
<tr>
<td>Immediate fatalities</td>
<td>All doses</td>
<td>&gt; 7000</td>
<td>&gt; 13 000</td>
</tr>
<tr>
<td>Radiation fallout (severity of health impact)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expectant care</td>
<td>≥ 10</td>
<td>18 000</td>
<td>45 000</td>
</tr>
<tr>
<td>Intensive care</td>
<td>5–10</td>
<td>19 500</td>
<td>79 400</td>
</tr>
<tr>
<td>Critical care</td>
<td>3–5</td>
<td>33 000</td>
<td>108 000</td>
</tr>
<tr>
<td>Normal care</td>
<td>1–3</td>
<td>66 000</td>
<td>70 000</td>
</tr>
<tr>
<td>Ambulatory monitoring</td>
<td>0.5–1</td>
<td>82 500</td>
<td>139 000</td>
</tr>
<tr>
<td>Epidemiological monitoring</td>
<td>0.25–0.5</td>
<td>106 000</td>
<td>147 000</td>
</tr>
<tr>
<td>Monitoring for mental health and psychological well-being with no other injury</td>
<td>&lt; 0.25</td>
<td>&gt; 150 000</td>
<td>&gt; 270 000</td>
</tr>
</tbody>
</table>

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a The assumptions include a city with a population of 2 million, and the numbers of casualties are estimated with the Hazard Prediction Assessment Capability Program, version 3.21 (Defense Threat Reduction Agency, Fort Belvoir (VA), USA).

b Combined injuries consist of radiation injuries in addition to burns or blunt trauma.
Radionuclide uptake inhibitors such as potassium iodide (KI) and decorporation agents should be administered as soon as possible after exposure or even prophylactically for KI. The following treatment approaches are applied for different radionuclides:

- Treatment is initiated before or shortly after exposure, such as administration of KI in cases of radioactive iodine release.
- Treatment is initiated before receiving the results of internal dose measurements, such as decorporation treatment with Prussian blue to remove caesium radionuclides.
- Treatment is based on the results of internal dosimetry, such as in use of decorporation therapy with diethylenetriaminepentaacetic acid (DTPA). In countries with limited capacity for internal dosimetry, use of this approach will be limited.

The duration of treatment should also be considered. In contrast to the widespread dispersal of infectious agents by personal proximity or contact, the spread of radioactive materials is usually limited to one area, depending on wind speed and direction. Therefore, a limited local stockpile may be sufficient for treatment of radiation injuries, assuming that manufacturers deliver pharmaceuticals and medical supplies according to their commitments or that international support is provided rapidly.

The objectives of protection in response to a radiation emergency are to avoid or minimize tissue effects (acute, subacute or delayed) and to reduce the risk of stochastic effects. In some cases, a large number of individuals may require treatment, and some may require months and years of treatment. It is difficult to provide a precise advice on the size of a national stockpile, as this requires reliable data for national risk profiles, the size of the populations that would be affected by specific scenarios and the health-care capacity of the country. Various approaches have been used to determine the scope and size of national stockpiles.

Scenario-based modelling may represent the most scientific approach for determining the size of a national stockpile, when data for each scenario relevant to the country (including data on the specific radionuclides involved in most relevant scenarios, geographical and demographic information, the potential extent of contamination, and other data) used to decide on the types and quantities of required MCM. In some cases, detailed modelling is not possible or is unnecessary, and simple assumptions may be used to estimate the quantity of a specific drug to be stockpiled. When the scope of radiation scenarios is defined, data obtained during past radiation incidents can guide a decision on the size of a national stockpile. The following scenarios may deserve particular attention.

- Exposure to radiation from a nuclear detonation has catastrophic consequences for the affected population and environment. In many countries, it may be considered an unlikely event; however, it was considered in designing a national stockpile, where a scenario for modelling the impact of a 10-kT bomb detonation in a large metropolitan area was proposed by a national agency in the USA as one of 15 scenarios for emergency response planning. The physical and radiological effects on affected areas and populations that would result from such a detonation have been studied in detail by state-of-the-art modelling and reliable assumptions, and guidelines for protective actions have been issued, such as evacuation, sheltering-in-place, dose projections and contamination of the environment. The modelled numbers of casualties in various categories are presented in Table 1. The medical response focuses on survival and prevention of major morbidity and requires the use of strategic national stockpiles to provide MCM and supplies.

- Exposure to an RDD presents other challenges, including initial characterization of radiological contamination, locating areas with non-uniform, high radiation and obtaining survey data to map the radioactivity over time.
• The severity of injury from an RED depends on the type and amount of radioactive material, the time a person spends near the device and the parts of their body that are exposed.

Table 2. Medical countermeasures applicable in four radiation emergency scenarios by isotopes involved

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Isotopes potentially involved</th>
<th>Main health effects</th>
<th>Most relevant pharmaceutical agent</th>
<th>No. of people potentially affected (according to previous experience or modelling data)</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPP accident</td>
<td>High impact: I, Cs</td>
<td>External and internal contamination, mental and psychological effects, increased risk of cancer</td>
<td>Iodine thyroid blocking with KI¹</td>
<td>Population in vicinity of nuclear installation - urgent protection zone (UPZ)</td>
<td>19, 24</td>
</tr>
<tr>
<td></td>
<td>Limited impact: Pu, Sr, many others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear detonation (≤ 10 kT)²</td>
<td>Numerous short half-life isotopes: e.g., I, Cs, Su, Pu, U</td>
<td>Mass casualties: fatalities, thermal burns, trauma, combined injuries, ARS, cutaneous radiation syndrome, mental effects, increased risk of cancer</td>
<td>CSFs for ARS patients; KI for emergency responders</td>
<td>≤ 200 000 people requiring critical care in a city with two million population</td>
<td>29, 30</td>
</tr>
<tr>
<td>Radiological dispersal device</td>
<td>Cs, Am, Su, I and other isotopes used in research; Ir, Co, Po, Pu and others may also be used.</td>
<td>External contamination with radioactive particles, dust, powder; wounds contaminated with radioactive shrapnel; mental and psychological effects</td>
<td>For internal contamination with - Cs: Prussian blue - Am, Pu: Ca DTPA, Zn DTPA; - Po: DMPS - Sr: alginates</td>
<td>In an accident in Goiânia, Brazil, &lt; 1% required decoloration with Prussian blue for internal contamination with radioactive isotopes of Cs. In a modelled scenario, 60 000 people might require DTPA treatment for 30 or 90 days¹</td>
<td>20, 23, 31</td>
</tr>
<tr>
<td>Poisoning with a radioactive isotope</td>
<td></td>
<td>Internal contamination (target organ depends on isotope); possibly lethal outcome with a emitters (e.g., Po-210 poisoning); increased risk of cancer</td>
<td></td>
<td>No available example because of wide variation in scenarios</td>
<td>21</td>
</tr>
<tr>
<td>Radiological exposure device ³</td>
<td>Any γ-emitter No isotope-specific treatment</td>
<td>May lead to high-dose whole-body external exposure and ARS. Number of people will depend on the scenario, the dose of radioactivity, the source/exposure rate and time spent in proximity</td>
<td>Cytokines and growth factors for ARS patients</td>
<td>Few accidental local exposures reported (e.g., mis-handled use of industrial radioactive sources of Ir-192 and Co-60). No modelling data was found for a deliberate scenario</td>
<td>N/A</td>
</tr>
</tbody>
</table>
National stockpiles for radiological and nuclear emergencies:  
policy advice

a A single dose after exposure during an NPP accident is considered sufficient. A 130 mg dose of stable iodine is recommended for adults below the age of 40 (see section 3.2.1). The estimate is derived from the UNSCEAR report in 2008 (19), which included the exposed public and workers (about 7 million) who were present in the contaminated areas after the Chernobyl NPP accident and individuals living farther away from the NPP (about 98 million). A conservative estimate of 100 million doses includes those living in distant areas beyond the UPZ where ITB will be administered. The numbers depend on population density and other factors. However, it would be highly unlikely to be exposed to radioactive iodine in doses justifying use of iodine thyroid blocking at distances much larger than predefined UPZ.

b Considerations for exposures resulting from a nuclear detonation are made for fallout only (residual radiation). In addition to the radiation exposure, significant trauma and thermal burns may occur. Early fallout consists primarily of radionuclides with a short half-life, requiring treatment of external irradiation and KI for emergency responders. Later fallout in the region and elsewhere consists of nuclides with short, intermediate or long half-lives, requiring public health measures such as restrictions of contaminated food and drinking water.

c Stockpile amounts are estimated as the daily dose of Prussian blue.

d It is unlikely that exposure from a radiological exposure device would lead to significant radionuclide incorporation. Therefore, management is considered only for potential cases of ARS. Treatment of ARS caused by external irradiation is similar for all radionuclides.
4. Stockpile formulary

4.1. Elements of a stockpile for radiation emergency

In addition to the generic medical supplies, such as trauma kits, fluids, painkillers, antibiotics, etc., radiation stockpile will include some specific elements – medicines and devices.

As specific medical products are required for a radiation emergency, it is important that product formulations make them amenable for rapid use in mass casualties. Thus, their route of administration should require minimal medical oversight, e.g., oral, subcutaneous, transdermal, inhaled or intramuscular rather than intravenous injection. Liquid formulations of oral products (or specific instructions for compounding tablets or capsules) for paediatric or geriatric use may be considered, if available. Further, dosing for children may not be calculated solely by weight. As storage considerations are important factors for the decisions on selecting the pharmaceutical products by the end-users (vendors, emergency response planners and managers, or a government stockpile managers and others), products that have minimal refrigeration requirements and long shelf-lives are preferred. Care must be taken to ensure that products that are stockpiled can be safely dosed in all populations, especially in children and pregnant women, and meet the other requirements as closely as possible.

Devices for assessing radiation dose and thereby for triaging large numbers of potentially exposed individuals, may have limited use in mass casualties, because of the requirements that devices be minimally invasive, rapid and radiation specific. Moreover, there is no universal portable device for measuring individual radiation dose for all types of radiation and all exposure pathways. The devices typically used in radiation emergencies are only mentioned briefly in this section for general information and not included in the scope of this document.
Other methods, such as biological, clinical, e.g., time to emesis, lymphocyte depletion kinetics (32), software tools (33), use of METREPOL criteria (34) and cytogenetic biodosimetry, can be extremely valuable. Rapid access to the necessary reagents and other laboratory consumables must be ensured from a local or a national stockpile or a commercial supplier in the case of an emergency to enable rapid diagnosis and dose assessment.

In addition, any public health emergency requires stockpiling of elements that are common to several threats, including personal protective equipment, trauma kits, antibiotics and other non-specific drugs, resuscitation fluids and items for palliative care. Therefore, it is important to explore the availability of other products that are already stockpiled and could be rapidly repurposed for a radiation emergency. In this document, only pharmaceutical products used in radiation emergencies are discussed.

The elements of a stockpile formulary are subject to national pharmaceutical regulation and approvals, and the regulatory status of MCM differs from country to country. Table 3 provides a summary of key MCM in some countries for which on-label and off-label regulatory approvals have been granted for radiological injury. Furthermore, the descriptions of each element of the stockpile below indicate whether it is on the WHO Essential Medicines List (EML).

Table 3. Regulatory status of key MCMs in selected countries (as of October 2022)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Canada</th>
<th>Germany</th>
<th>France</th>
<th>United Kingdom</th>
<th>Japan</th>
<th>Russia Federation</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium iodide</td>
<td>+(^a)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Prussian blue</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–(^b)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ca or Zn DTPA</td>
<td>–(^b)</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Alginates</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Aluminium antacids</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>(Peg) Filgrastim (G-CSF)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Sargramostim/Molgramostim (GM-CSF)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Romiplostim</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

\(^a\) Approved as MCM for radionuclide incorporation or radiation injury-related indication (on-label)

\(^b\) Approved but discontinued (e.g., by manufacturer)

\(0\) Approved for other conditions not related to radionuclide incorporation or radiation injury (off-label)

\(-\) No current approval

G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte and macrophage colony stimulating factor; PEG, pegylated
\(^a\) As a natural health product
\(^b\) Imported through a special access programme
4.2 Internal contamination

Exposure to radiation by inhalation, ingestion or a contaminated wound could result in incorporation of radionuclides into the body tissues and organs, which could have immediate or lingering health effects. Different radionuclides target different organs (see Fig. 1) and behave differently in the human body. Fortunately, blocking agents (such as potassium iodide) prevent incorporation of radionuclides, and decorporation treatments (such as chelation) remove them and thus reduce the burden, reducing radiation-associated risk for health effects (35).

Figure 1. Primary target organs for common internal emitters
Although several approaches are currently available, they cover only a limited range of radionuclides, and some require repeated intravenous administration. Investment in research has, therefore, been made to develop novel products with routes of administration that are more amenable to treatment of large populations (see section 6.1). Use of existing decorporation and blocking agents for prevention and management of internal contamination is discussed below.

4.2.1 Blocking agent

**Potassium iodide (KI)**

**Context:** Radioactive iodine may be released in a plume or cloud during a nuclear accident, contaminating the environment. Inhalation of contaminated air and ingestion of contaminated food and drinking-water may lead to internal exposure and uptake of radioactive iodine, mainly by the thyroid. Increased risk of thyroid cancers in persons exposed to radioactive iodine at the age of 0 to 18 is the main pathological consequence. Oral administration of stable iodine, usually as KI tablets (with control of food and drinking-water) is referred to as iodine thyroid blocking (ITB) and is considered an appropriate strategy for reducing the risk of thyroid cancer in people exposed to accidental release of radioactive iodine. It is included in many Member States’ preparedness plans. Guidance on appropriate use of KI has been issued by WHO and others, which indicates that KI is relatively safe and effective if given in a timely fashion (35, 36).

**Table 4. Recommended dosing of KI by age group (35)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Mass of iodine, mg</th>
<th>Mass of KI, mg</th>
<th>Fraction of a 130 mg tablet*</th>
<th>Fraction of a 65 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates (birth to 1 month)</td>
<td>12.5</td>
<td>16</td>
<td>1/8</td>
<td>1/4</td>
</tr>
<tr>
<td>Infants (1 month to 3 years)</td>
<td>25</td>
<td>32</td>
<td>1/4</td>
<td>1/2</td>
</tr>
<tr>
<td>Children (3–12 years)</td>
<td>50</td>
<td>65</td>
<td>1/2</td>
<td>1</td>
</tr>
<tr>
<td>Adults and adolescents (&gt; 12 years)</td>
<td>100</td>
<td>130</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Some manufacturers use 125 mg KI tablets, which contains the similar mass of iodine
**Effect:** The efficacy of therapy depends on the pharmacokinetics of radioactive iodines. Iodines are rapidly and completely absorbed as iodides. Radioactive iodines, mainly $^{131}I$, concentrate in the thyroid gland due to carrier-mediated transport by the Na–I symporter, and administration of stable iodine results in symporter blockade, which limits the uptake of radioactive iodines by the thyroid and the duration of internal irradiation. If stable iodine is administered before or at the onset of exposure to radioactive iodine, its uptake will be blocked due to saturation of the thyroid gland with stable iodine, thus effectively reducing internal exposure of the thyroid. The optimal period of administration of stable iodine is $< 24$ h before and $\leq 2$ h after the expected onset of exposure.

**Contraindications:** Hypersensitivity to KI may be considered a contraindication. Otherwise, apart from a few rare pre-existing immunological diseases (dermatitis herpetiformis or hypocomplementaemic vasculitis), there is no contraindication to oral administration of KI.

**Side-effects:** Risk groups for adverse reactions include those with pre-existing thyroid disorders and iodine hypersensitivity. Thyroidal side-effects may be frequent in patients with pre-existing thyroid disease, e.g., Graves disease or functional autonomous “hot” thyroid nodules, which may develop with age in adults living in iodine-deficient areas. Extra-thyroidal side-effects are rare for the mildest cases and exceptional for the most severe cases (digestive disorders in $< 2\%$ of cases, with vomiting, diarrhoea and gastric pain, and mild skin rashes in $< 1\%$ of cases).

**Stability and storage:** Tablets packed in hermetic packaging and kept in a dry, cool place fully preserve their iodine content for 5 years. After 5 years, the iodine content should be checked and the shelf-life extended as necessary, if a formal protocol for testing such extensions has been established and validated. The shelf-life can be further extended under the same conditions (37).

### 4.2.2 Decorporating agents

**Context:** accidental inhalation or ingestion of certain radionuclides will lead to internal contamination, where various radionuclides will target various tissues and organs. Some of them may enter bloodstream and be deposited in target organs (see Fig.1) and cause systemic or local radiation effects. In such cases, decorporation therapy is used to reduce absorption from the gastrointestinal tract, or to use isotopic dilution, diuretics, adsorbents, and chelating agents to remove the radionuclides from the body. For example, oral Prussian blue capsules are approved in some countries for treatment of internal contamination with radioactive caesium, and Ca and Zn DTPA, administered intravenously or by nebulizer, to treat contamination with transuranic radionuclides (e.g., Pu, Am and Cm) (36).

**Prussian blue (PB)**

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>$\text{Fe}^{III}<em>{4}[\text{Fe}^{II}(\text{CN})</em>{6}]<em>{3} \times \text{H}</em>{2}\text{O}$, ferric ferrocyanide, PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Potassium ferric hexacyanoferrate is included for other indications.</td>
</tr>
<tr>
<td>Indication</td>
<td>Incorporation of radioactive Cs isotopes, Tl intoxication</td>
</tr>
<tr>
<td>Route of application</td>
<td>Oral, 500 mg capsules or tablets</td>
</tr>
<tr>
<td>Dosing</td>
<td>Usually 3 x 1 g/day for 30–90 days</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>Usually 5 years, shelf-life extension technically possible</td>
</tr>
</tbody>
</table>
Specific dosing: The usually recommended dosing for radiocaesium intoxication is 3 g/day distributed as equally as possible over 24 h (usually 1 g every 8 h). Dosing of up to 20 g/day is considered safe. Various dosing intervals have been proposed. An initial dosing > 3 g is considered reasonable within several hours of ingestion. After inhalation, the excretion rate depends on the amount of Cs secreted into the enterohepatic circulation (45) and initial high dosing, therefore, provides no benefit. Furthermore, obstipation, a potential side-effect of high doses, could lead to longer retention time of Cs in the gut and thus higher doses of radiation to the gastrointestinal tract. A liquid formulation of Prussian blue is being developed for paediatric or geriatric use when there is difficulty in swallowing large capsules (38).

Treatment initiation: The earlier Prussian blue therapy is started, the more efficient it is in early removal of radionuclides. The effective dose is reported to be reduced by 61% if therapy is started within the first day and by 53% if started on day 10. Its efficacy can be enhanced by increasing the duration of treatment, but compensation for a delay in treatment initiation by longer therapy is limited.

Duration of therapy: The duration of therapy with Prussian blue depends on the extent of contamination but is not less than 30 days, according to the manufacturer. Efficacy appears to be further enhanced with up to 90 days of treatment, before reaching a plateau (39). Regular measurements of the remaining Cs activity are recommended to monitor the effect of therapy.

Effect: Prussian blue administered orally (40) acts as an ion scavenger in the gut. It is not absorbed by the gastrointestinal tract, but it binds Cs ions in the gut, thereby enhancing faecal excretion. The faecal/urinary excretion ratio without Prussian blue therapy was reported to be 0.15, whereas, with Prussian blue therapy, it increased up to four times (depending on dosage) (40). Prussian blue reduces the biological half-time of radiocaesium by about 65% in adults (41).

Stability and storage: Prussian blue is stable at room temperature. The product used in the European Union and the USA is approved by the European Medicines Agency and the US Food and Drug Administration (FDA) for 5 years of shelf-life.

As Prussian blue is barely absorbed in the gastrointestinal tract, the major concern with longer storage of Prussian blue would be development of hazardous degradation products, which could be absorbed. The main degradation product of concern is hydrogen cyanide, as cyanide makes up 35–40% of Prussian blue (depending on the water of crystallization) (42). During storage for 10 years under ambient conditions (20–22 °C, 40–60% relative humidity), Prussian blue was thermodynamically stable but had lost bound water. The release of cyanide is not, however, increased to an extent that would obviate usage: the dose released under vastly pessimistic conditions in vitro was about 75 µg/g, which would result in a maximum exposure of 1.5 mg cyanide if the maximum dose of 20 g Prussian blue were given (human maximum tolerated dose, 14.4 mg for a 70-kg male) (43). The Cs-binding capacity, however, decreased significantly with loss of bound water to 265 mg/g instead of 358 mg/g after 10 years of storage (44) (the US FDA specification for the Cs binding capacity of Prussian blue is > 150 mg/g).
### Chelating agents: Ca DTPA and Zn DTPA

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Ca- or Zn- diethylenetriamine pentaacetate. CaNa(_2)DTPA: Ca DTPA ZnNa(_2)DTPA: Zn DTPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Not included</td>
</tr>
<tr>
<td>Indication</td>
<td>Decorporation of transuranium elements or other polyvalent cationic elements</td>
</tr>
<tr>
<td>Route of application</td>
<td>Typically intravenous infusion, inhalation (for decorporation of inhaled radionuclides) and topical application (for wound decontamination) have been described (36). Oral formulations have been studied but were shown to be insufficiently effective (45, 46).</td>
</tr>
<tr>
<td>Dosing</td>
<td>1 g daily for 5 days; 2–3 injections per week for 6 weeks followed by a break, total duration depending on response</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>5 years for sterile product when stored at 15–30 °C</td>
</tr>
</tbody>
</table>

**Detailed indication**: Used for decorporation of transuranium elements (Am, Pu, Cm, Cf, Bk) (47) and of Ac, Ce, Cr, Co, Es, Eu, In, La, Mn, Nb, Pd, Ru, Sc, Th, Y, Zn, Zr and Pm (48). It is not recommended (although effective) for decorporation of U, Np or Cd because of its potential to cause nephrotoxicity.

**Specific dosing**: The initial dose for adults is 1 g daily for the first 5 days (15 mg/kg per day; 1 ampoule). After 5 days, the dosing interval can be lengthened to two or three injections weekly for 6 weeks. For children under 12 years, 14 mg/kg is recommended, not to exceed 1 g (47). Depending on the therapeutic response, a 6-week break without therapy may be recommended. Therapy can then be alternated in a schedule of 3 weeks with and 3 weeks without therapy until a plateau in averted dose has been achieved.

A DTPA solution is added to 20 mL of physiological saline solution or 5% glucose solution and administered over 15 min. Another well-tolerated treatment is infusion of 1 g in 250 mL diluent over 30–120 min. For wounds contaminated with an actinide, irrigation with DTPA may be considered, with a solution such as 1 g Ca DTPA and 10 mL 2% lidocaine in 100 mL of normal saline. For inhalation therapy, 1 g of DTPA is prepared in a 1:1 dilution with sterile water or normal saline.

**Time of treatment initiation**: DTPA should be administered as soon as possible after exposure, ideally within the first 24h. If early administration is not possible, therapy can be initiated at any time; however, the efficacy decreases substantially when radionuclides are deposited in the bone and other organs (47, 48). Within the first 24h after incorporation, Ca DTPA removes radionuclides faster than Zn DTPA because of its greater binding affinity (~10 x) for the transuranium elements. Afterwards, if possible, therapy should be changed to Zn DTPA, as it scavenges fewer essential trace elements from the body. If Zn DTPA is not available, Ca DTPA can be administered as prolonged therapy, together with replacement of zinc (47, 48). If Ca DTPA is not available for the first dose, Zn DTPA may be administered (47, 49).

**Duration of therapy**: The duration of therapy depends on the amount and type of radioisotope. Urinary radioisotope levels should be monitored regularly, and treatment should be continued if the excretion rate increases. In most cases, therapy for the first 5 days will eliminate most incorporated transuranium radionuclides from the body. When protracted treatment with DTPA is required, endogenous metals (e.g., Zn, Mg, Mn) and their related enzymes in serum should be monitored, and mineral supplements containing Zn should be considered. Alkaline phosphatase is a good indicator of imbalance of essential metals during DTPA treatment (50).

**Effect**: DTPA forms water-soluble chelate complexes with many polyvalent cations (such as the transurananes), thus enhancing the solubility and therefore, the urinary excretion rate. Nephrotoxic radionuclides such as U should not be decorporated with DTPA in order to avoid damage to the kidney. Oral bioavailability
National stockpiles for radiological and nuclear emergencies: policy advice

is < 10%, and inhalation as an aerosol will result in a bioavailability of 20–30%. DTPA can reduce the absorbed dose of soluble forms of Pu and Am (such as PuO₂(NO₃)₂·22 H₂O) by 80% if given within 24 h (48). In contrast, oxides such as PuO₂ preferentially deposit in the lungs, where, depending on particle size, they may reside for months, as well as in thoracic lymph nodes, liver and bone. The beneficial effect of DTPA in such cases is < 25%.

Ca-DTPA is contraindicated in the nephritic syndrome or in cases of renal insufficiency (48). As Ca DTPA is teratogenic, only Zn DTPA is administered during pregnancy.

Aluminium-containing antacids and alginates

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>AIPO₄, aluminium phosphate, sodium alginate</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Not included</td>
</tr>
<tr>
<td>Indication</td>
<td>Ingestion of radioactive Sr</td>
</tr>
<tr>
<td>Route of application</td>
<td>Oral</td>
</tr>
<tr>
<td>Dosing</td>
<td>100 mL aluminium phosphate gel or 10 g sodium alginate</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>Suspensions of aluminium phosphate: 3 years; suspensions of alginate: 2 years</td>
</tr>
</tbody>
</table>

Specific Dosing and duration of therapy: 100 mL aluminium phosphate gel (no beneficial effect on higher doses or 10 g of sodium alginate are given daily for several days. Therapy is initiated before or within 2 h of intake for the optimal effect; the absorbed dose increases if given later. After full gastrointestinal uptake of ingested Sr, the achievable effect is minor (48).

Effect: Aluminium-containing antacids have been shown to increase the Sr excretion rate if applied shortly before or within 2 h of oral uptake of radionuclides of Sr in humans (48). Alginate is provided as sodium alginate, and the Na is exchanged for Sr, which is also excreted. Alginates have the advantage of being also approved for antacid therapy in children and pregnant women.

Stability and storage: Suspension of alginates for oral intake have a shelf-life of 2 years, as stated by the manufacturer; suspensions of aluminium phosphate have a stated shelf-life of 3 years. If the active substance is stored alone, instead of the drug product, the recommended date for retesting the active substance is 5 years.

Sodium bicarbonate

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>NaHCO₃, sodium hydrogen carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Included for parenteral use in other indications</td>
</tr>
<tr>
<td>Indication</td>
<td>Internalization of radioactive U</td>
</tr>
<tr>
<td>Route of application</td>
<td>Intravenous infusion, oral</td>
</tr>
<tr>
<td>Dosing</td>
<td>Intravenous: max. 1.5 mmol/kg body weight per h; oral: 2 tablets (1.0–1.3 g) every 4 h</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>Intravenous: 2 years; tablets: 3 years</td>
</tr>
</tbody>
</table>

Specific dosing and duration of therapy: Sodium bicarbonate for intravenous application is commonly supplied as a 4.2% (500 mM) or an 8.4% (1 M) solution, although other concentrations are available. Little information was available on use in U intoxication, but infusions up to 1.5 mmol/kg body weight within 1 h are considered safe and can be given in either 1 L of 0.9% NaCl solution or in 5% glucose in water. The volume can be lowered to 250 mL, although the infusion rate of 1.5 mmol/kg body weight should not be exceeded.
For oral administration, sodium bicarbonate is commonly provided as antacid tablets in doses ranging from 500 to 650 mg. Two tablets every 4 h is considered safe. Urinary pH is monitored hourly during treatment to maintain a range of 8–9 (51). The daily dose is adjusted to this therapeutic goal, and therapy is continued for 3 days.

Some reports indicate that sodium bicarbonate may induce hypokalaemia and respiratory acidosis (48), therefore treatment should be given under careful control, including a comprehensive metabolic panel of blood tests, K levels, electrocardiography and urinalysis.

Effect: Sodium bicarbonate alkalizes the urine and forms predominantly uranyl tricarbonate at a pH ≥ 8. This stable complex is considered to interact less with renal tubular cells and was thus less nephrotoxic in rats (51).

Stability and storage: For sodium bicarbonate solution for infusion, the limiting factor for a 1-M solution is its microbiological stability, which limits its recommended use to 2 years at room temperature. After dilution to a ready-to-use concentration, its physicochemical stability is reduced to 7 days when refrigerated and 30–48 h at room temperature, depending on the concentration (52).

For oral administration, sodium bicarbonate tablets have a shelf-life of 3 years at room temperature. The pure substance should be retested after 3 years.

4.3 Acute radiation syndrome

Exposure to a high dose of ionizing radiation may result in ARS, manifested as haematopoietic, gastrointestinal, cardiovascular and neurological syndromes (Figure 2). This document addresses treatment of the first two (hematopoietic and gastrointestinal), as cardiovascular and neurological syndromes are considered non-salvageable, and patients require only palliative care.

Figure 2. Dynamics of the neutrophil count in prereferral blood depending on the level of radiation dose (34)
4.3.1 Agents for the management of haematopoietic injury

Context: Certain pharmaceutical products used to treat other clinical conditions are also effective in the management of radiation-induced injuries, including ARS and local radiation injuries (53) and have been approved for ARS management in some countries. For instance, growth factors (i.e., cytokines) that target myeloid cells (i.e., granulocytes) (G-CSF) or granulocytes and macrophages (GM-CSF) enhance proliferation of granulocytic or granulocyte–macrophage progenitors, facilitate myeloid maturation, protect against programmed cell death (i.e., apoptosis) and enhance cell function (54, 55). Clinical management of radiation-induced acute haematopoietic injury with growth factors has been reviewed (56). Myeloid growth factors have been developed as MCM to treat acute and delayed injuries from exposure to radiation to mitigate radiation-induced neutropenia. They are approved by the US Food and Drug Administration (FDA) for treatment of acute radiation syndrome, and filgrastim, pegfilgrastim and sargramostim are included in the US stockpile for use in mass casualty emergencies (57, 58). Another growth factor, romiplostim, which mitigates radiation-induced thrombocytopenia by increasing platelet production in the bone marrow, was later approved by the US FDA for ARS treatment (59) and included in the US stockpile. Romiplostim is a fusion protein that binds to the thrombopoietin receptor and stimulates megakaryopoiesis and thrombopoiesis. Its activity is complementary to the biological effects of myeloid growth factors and cytokines, and it is therefore used in combination with the other cytokines.

Erythropoietin, a growth factor currently used in clinical management of anaemia (60), is also administered to mitigate radiation-induced anaemia and reduce the need for blood transfusion (see section 6.1). Haematopoietic stem cell therapy (SCT) can be considered for patients who have failed a ≥ 2-week trial of supportive haematological care, including cytokine therapy and transfusions, and who have limited, potentially curable injury to non-haematopoietic organ systems (61). Although SCT falls outside the scope of this document, a short description is provided in Box 2 for informational purposes.

Box 2. Haematopoietic stem cell transplantation

Haematopoietic SCT is not generally recommended for the treatment of radiation injury. Most experience in use of this treatment was gained in treating victims of the Chernobyl nuclear power accident in 1986 (53). Unfortunately, most of the patients also had additional (non-haematopoietic) organ injury, and the mortality rate was high. A review of this and other radiation incidents showed that 27 of 31 patients who underwent haematopoietic SCT died, and the four remaining patients survived with a rejected allograft (53, 62). Therefore, SCT should only be considered when all other treatment options have failed.
Granulocyte colony-stimulating factor (G-CSF)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Filgrastim (no glycosylation), Lenograstim (with glycosylation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Filgrastim is included, Lenograstim is not included</td>
</tr>
<tr>
<td>Indication</td>
<td>Irradiation expected to result in haematopoietic injury</td>
</tr>
<tr>
<td>Route of application</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Dosing</td>
<td>10 µg/kg body weight</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>Filgrastim: 3 years if stored at 2–8 °C</td>
</tr>
<tr>
<td></td>
<td>Lenograstim: 2 years if stored at 2–8 °C</td>
</tr>
</tbody>
</table>

**Specific dosing:** For individuals exposed to ionizing radiation resulting in or expected to result in haematopoietic injury, a dose of 10 µg/kg of G-CSF is administered subcutaneously, once daily, as soon as possible after a suspected or confirmed radiation dose of > 2 Gy (63). Treatment continues until the absolute neutrophil count is > 1000/mm³ on three occasions or is > 10 000/mm³. In infants and children, a dose of approximately 3 µg/kg body weight per day may be used. Rounding the dose to the nearest vial size may maximize the cost–benefit ratio. No dose-limiting toxicity has been observed.

**Side-effects:** After an intravenous bolus injection, G-CSF induces transient leukopenia within 30 min. Bone and musculoskeletal pain, presumably due to an expanding myeloid compartment within the marrow, occurs in about 20% of cancer patients; it is partly relieved by nonsteroidal anti-inflammatory therapy. Other side-effects are fever, chest pain, cough, nausea, fatigue, skin rash, thrombocytopenia and a requirement for more frequent liver function tests in > 10% of recipients. Splenomegaly has been reported, and splenic rupture may occur in rare cases (64).

Pegylated granulocyte colony-stimulating factor (PEG-G-CSF)

| Drug name                  | Pegfilgrastim                                                   |
|----------------------------|                                                               |
| EML 2021                   | Not included                                                   |
| Indication                 | Irradiation expected to result in haematopoietic injury        |
| Route of application       | Subcutaneous injection                                         |
| Dosing                     | 6 mg/week                                                       |
| Shelf-life                 | 3 years if stored at 2–8 °C                                     |

**Specific dosing:** The typical dose of PEG-G-CSF for individuals exposed to ionizing radiation resulting in haematopoietic injury is 6 mg/week (65). Although a baseline complete blood count (CBC) is advised, a delay in administration is not justified if CBC not readily obtainable. The first dose is administered as soon as possible after suspected or confirmed exposure to > 2 Gy radiation. The second dose is administered 1 week after the first.

**Side-effects:** Bone pain (osteoalgia) and musculoskeletal pain, presumably due to an expanding myeloid compartment within the marrow, occurs in about 20% of cancer patients, and is partly relieved by nonsteroidal anti-inflammatory therapy. Other side-effects, which occur in < 1% of individuals, include anaphylaxis, severe hypersensitivity reaction, capillary leak syndrome, acute respiratory disease syndrome, glomerulonephritis, skin infiltration of granulocytes (Sweet syndrome), sickle cell crisis and, rarely, splenic rupture.
Granulocyte–macrophage colony stimulating factor (GM-CSF)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Sargramostim</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Not included</td>
</tr>
<tr>
<td>Indication</td>
<td>Irradiation expected to result in haematopoietic injury</td>
</tr>
<tr>
<td>Route of application</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Dosing</td>
<td>7 µg/kg body weight for adults</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>Not indicated by the manufacturer, storage at 2–8 °C</td>
</tr>
</tbody>
</table>

**Specific dosing:** The typical dose of GM-CSF for adults exposed to ionizing radiation resulting in haematopoietic injury is > 40 kg, with 7 µg/kg administered subcutaneously once daily, beginning as soon as possible after suspected or confirmed exposure to a radiation dose > 2 Gy, even in the absence of a baseline CBC. Off-label, 250 µg/m²/day can be injected subcutaneously and continued until the absolute neutrophil count is > 1000/mm³ (15). The guidelines of the American Society of Clinical Oncology (ASCO) recommend initiation within 24 h of exposure to a dose ≥ 2 Gy and/or a significant decrease in absolute lymphocyte count or for anticipated neutropenia < 500/mm³ for ≥ 7 days (66). The typical dose of GM-CSF is 250 µg/m² per day by subcutaneous injection. The dose may be rounded to the nearest vial size to maximize the cost–benefit ratio.

**Side-effects:** After an intravenous bolus injection, GM-CSF induces transient leukopenia within 30 min. GM-CSF may induce flu-like symptoms (i.e., malaise, fever, myalgia, arthralgia and headache), rash and abnormalities in liver function tests in > 10% of cases. The effects are usually mild, are alleviated by antipyretics and disappear with continued administration.

Systemic toxicity has been observed with GM-CSF at doses > 32 µg/kg per day intravenously or > 15 µg/kg per day subcutaneously, including capillary leak syndrome, phlebitis and venous thrombosis may also occur (67). Skin infiltration by granulocytes may lead to acute febrile neutrophilic dermatosis and necrotizing vasculitis (68).

Romiplostim

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Romiplostim</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Not included</td>
</tr>
<tr>
<td>Indication</td>
<td>Irradiation expected to result in thrombocytopenia</td>
</tr>
<tr>
<td>Route of application</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Dosing</td>
<td>10 µg/kg body weight</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>5 years as lyophilisate if stored at 2–8 °C</td>
</tr>
</tbody>
</table>

**Dosing:** The typical dose of Romiplostim for individuals exposed to ionizing radiation resulting in or expected to result in haematopoietic injury is a single dose of 10 µg/kg (59). Treatment should be initiated as soon as possible after suspected or confirmed exposure to radiation at > 2 Gy, regardless of the availability of a baseline CBC.

**Side-effects:** Skin rash, abdominal pain, diarrhoea, acute myelocytic leukaemia, nervous system symptoms (headache, dizziness and insomnia), arthralgia and myalgia have been reported in adults and bruising, oropharyngeal pain, upper respiratory tract infections and fever in children and adolescents, each at a reported frequency of > 10%.
4.3.2 Agents for management of gastrointestinal Injury

Context and indications: Ionizing radiation at doses $\geq 5$ Gy induces breakdown of the gastrointestinal mucosal barrier and altered structural integrity of the gastrointestinal tract, predisposing translocation of enteric bacteria into the circulation, severe secretory diarrhoea, dehydration and electrolyte imbalance, all of which contribute to a high mortality rate \cite{69}. Although several radiation-specific therapeutics are being investigated, none has been approved by regulatory bodies for treatment of radiation injury to the gastrointestinal tract. The mainstays of management of acute gastrointestinal radiation injury, in addition to replacement of fluids and electrolytes, include administration of antiemetic compounds, anti-diarrhoeal drugs and antimicrobial agents \cite{70}.

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML 2021</td>
<td>Included</td>
</tr>
<tr>
<td>Indication</td>
<td>Antiemetic therapy</td>
</tr>
<tr>
<td>Route of application</td>
<td>Intravenous infusion, orally as melting tablets or film tablets</td>
</tr>
<tr>
<td>Dosing</td>
<td>Intravenous: 8 or 0.15 mg/kg body weight; oral: 8 mg once or twice daily</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>Sterile intravenous and oral forms: 3 years</td>
</tr>
</tbody>
</table>

The antiemetic of choice is a selective serotonin-receptor antagonist, 5-hydroxytryptamine (Ondansetron).

Dosing: As centrally mediated nausea and vomiting may occur at radiation doses $< 5$ Gy, antiemetic therapy is used in individuals exposed to doses $\geq 2$ Gy \cite{70}. The doses for adults are intravenous administration, 8 or 0.15 mg/kg (maximum, 16 mg/dose [manufacturer’s labelling]) once or twice daily; oral administration: 8 mg once or twice daily as required. The appropriate duration of antiemetic therapy after radiotherapy is not well defined; the ASCO recommends continued administration once or twice daily on the day after each radiation session \cite{71}. For children receiving total body irradiation for haematopoietic stem cell transplantation, oral doses of 4 mg every 8 h are given throughout irradiation to children aged 4–11 years and 8 mg every 8 h for adolescents $\geq 12$ years. Patients should be monitored continually for persistent nausea and vomiting to determine whether further Ondansetron is required.

Side-effects: Ondansetron may cause constipation, headache, fatigue, malaise, hypersensitivity reactions and electrocardiographic abnormalities, including prolongation of the QT interval and bradycardia. Ventricular arrhythmia and torsades de pointes have been reported, as well as rare fatalities.
Diarrhoea can be controlled with common anti-diarrhoeal drugs such as loperamide hydrochloride and diphenoxylate–atropine. Loperamide was identified as initial therapy due to its greater efficacy and better toxicity profile (70).

**Specific dosing:** In adults, the initial oral dose is 4 mg, followed by 2 mg after each loose stool, with a maximum dose of 16 mg/day (manufacturer’s labelling) (72). The maintenance oral dose, the lowest required to control symptoms, is usually 4–8 mg/day as a single dose or in divided doses (e.g., 2 mg before meals) (73). If no clinical improvement is observed after ≥ 10 days of the maximally tolerated dosage, symptoms are unlikely to be controlled by further administration.

In children, the lowest effective oral dose should be used for the shortest duration. For children aged 2–5 years weighing 13–20.9 kg, the initial dose is 1 mg after the first loose stool, followed by 1 mg/dose after each subsequent loose stool for a maximum daily dose of 3 mg/day. For children aged 6–8 years weighing 21–27 kg, the initial dose is 2 mg after the first loose stool, followed by 1 mg/dose after each subsequent loose stool for a maximum daily dose of 4 mg/day. For children aged 9–11 years and weighing 27.1–43 kg, the initial dose is 2 mg after the first loose stool, followed by 1 mg/dose after each subsequent loose stool for a maximum daily dose of 6 mg/day. For adolescents aged ≥ 12 years, the initial oral dose is 4 mg after the first loose stool, followed by 2 mg/dose after each subsequent loose stool for a maximum daily dose of 8 mg/day (72). As with all medications, patients should be monitored routinely to determine continued administration of loperamide.

**Side-effects:** In 1–10% of cases, the following side-effects were observed: dizziness, constipation, abdominal cramps and nausea. Other side-effects that have been reported include drowsiness, dyspepsia, erythema multiforme (rare), fatigue, flatulence, megacolon, paralytic ileus, pruritus, skin rash, Stevens-Johnson syndrome (rare), anaphylaxis (rare) and anaphylactic shock (rare). Cases of torsades de pointes, cardiac arrest and death have been reported with doses higher than those recommended.

**Contraindications:** Loperamide is contraindicated in patients < 2 years of age.

### Loperamide

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Loperamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>WML 2021</td>
<td>Included</td>
</tr>
<tr>
<td>Indication</td>
<td>Anti-diarrhoeal therapy</td>
</tr>
<tr>
<td>Route of application</td>
<td>Oral</td>
</tr>
<tr>
<td>Dosing</td>
<td>Initial dose: 4 mg; maximum, 16 mg/day for adults</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>5 years</td>
</tr>
</tbody>
</table>

**Context:** Ionizing radiation suppresses the production of haematopoietic cells by the bone marrow in a dose-related fashion. Patients with prolonged neutropenia are at increased risk of opportunistic and nosocomial infections and may benefit from prophylactic antimicrobial therapy (15, 56, 70), including antibiotic, antifungal and antiviral agents. Patients with an absolute neutrophil count of < 0.5 x 10⁹/L can be presumed to have received an absorbed dose of > 2 Gy, placing them at risk for gastrointestinal tract injury with bacterial translocation across the bowel wall, sepsis and death. The goal of antimicrobial prophylaxis for these patients is to achieve therapeutic systemic and tissue drug levels rather than bowel decontamination.
The choice of antibiotics depends on the antimicrobial spectrum, local resistance patterns, monitoring requirements, toxicity, allergic reactions and logistics of administration. Use of antimicrobials is based on the degree of leuko- and neutropenia and the expected duration of immunosuppression, as recommended by the Infectious Diseases Society of America (74) and the European Society of Medical Oncology (75) for use of antimicrobials in febrile neutropenia after chemotherapy and of the WHO AWaRe Antibiotic Book (76). The choice of antifungal agents depends on their availability, their toxicity and interactions, the type of infection suspected and local epidemiology. A detailed discussion is beyond the scope of this publication. Empirical use of antiviral agents is considered in patients with a medical history of a herpes simplex virus infection and in those who are seropositive for herpes simplex (15) or cytomegalovirus. An infectious diseases specialist should be consulted for an invasive fungal infection or if dissemination of herpes simplex virus or cytomegalovirus disease is suspected.

Candidates for prophylactic antimicrobial therapy include patients with fever or an oral temperature ≥ 38.3 °C (or ≥ 38.0 °C for patients with an absolute neutrophil count < 0.5 x 10⁹/L); patients with afebrile neutropenia with clinical signs and symptoms of infection; and patients with clinical signs and symptoms of infection without neutropenia (75). An empirical antibiotic regimen of ciprofloxacin or amoxicillin/clavulanate may be used for ambulatory “low-risk” patients with an expected duration of immunosuppression of days to weeks and/or whose absolute neutrophil count is < 0.5 x 10⁹/L but > 0.1 x 10⁹/L. This regimen provides broad-spectrum coverage of Gram-positive streptococci and staphylococci and Gram-negative Pseudomonas and Enterobacteriaceae.

Hospitalization is indicated for people who require intravenous antibiotics for documented infections and for people who cannot tolerate oral therapy because of persistent vomiting. Patients with profound neutropenia (i.e., an absolute neutrophil count of < 0.1 x 10⁹/L) and/or major comorbid medical conditions (i.e., haemodynamic instability, severe mucositis, gastrointestinal symptoms, mental status changes, intravenous catheter infections, new pulmonary infiltrates, underlying chronic lung disease or hepatic or renal insufficiency) require hospitalization for parenteral administration of antibiotics. These “high-risk” patients have an expected duration of immunosuppression of weeks to months and are treated with a single intravenous antibiotic (i.e., a fourth-generation cephalosporin such as cefepime or ceftazidime, carbapenem or piperacillin/tazobactam), until the results of cultures, imaging tests and clinical course are defined (69). Adjustment of the antibiotic regimen is dictated by the resulting clinical, imaging and culture findings. For documented infections, antibiotics are continued as indicated by the organism and site of infection, and at least until the absolute neutrophil count exceeds 0.5 x 10⁹/L (15).

### 4.3.4 Delayed effects of acute exposure to radiation

In most scenarios of exposure to radiation, haematopoietic and gastrointestinal tract injuries are responsible for early deaths, although, if individuals are shielded in some way by structures, they may survive exposure to higher doses in the short term. People who either survive ARS or receive sublethal exposure might then be susceptible to late tissue damage, referred to as the “delayed effects of acute radiation exposure”. The outcomes include late lung injuries, renal damage, ocular injuries like cataract formation and neurological outcomes such as cognitive deficits. Delayed effects of acute radiation exposure are not to be confused with the known stochastic effects of radiation, which include increased risks of certain types of cancer. When products to mitigate and/or treat delayed effects of acute radiation exposure, such as pulmonary and kidney injuries, become available for stockpiling, they will increase the options for treating casualties after a radiation incident. Some products to address certain late outcomes are being studied (see section 6.1).
The development and management of any emergency stockpile is complex, involving many sectors and elements, such as risk mapping and prognosis (based on assumptions, modelling or research results), planning and budgeting, procurement (including quality control, quality assurance and the safety of the product), legislation on procurement (approval of medical products and devices), ensuring financial sustainability and supply chain (e.g., several suppliers and contractors), investment in training of the workforce, storage and service delivery, monitoring and evaluation (77). Many of these elements are generic, and some may not apply to radiation emergency stockpiles. This section describes key elements for assisting policymakers and managers during the development of a national stockpile for radiation emergencies and the relevant procedures and protocols.

5.1 Governance and management of a generic stockpile

Assumptions and development of a stockpile

The size and composition of a stockpile are determined by assumptions about the anticipated types of radiation emergencies. For example, authorities would be stockpiling and/or distributing KI in areas near an NPP within or near another Member State’s border. Others may decide to increase the availability of cytokine or growth factors if they are concerned about the risk of a nuclear detonation.

Bilateral or regional agreements with neighbouring countries to share national stockpiles may be considered when planning response, especially for countries with a low risk of radiation emergencies, which may choose not to invest in stockpiling the pharmaceuticals required for clinical management of radiation injuries.
**Stockpile management**

Maintenance of the stockpile requires continual monitoring and evaluation. The formulary must be regularly reviewed and updated to reflect state-of-the-art management and include advances in logistics, transport and storage. Quality assurance and quality control measures must be applied continually to maintain the currency, accuracy and completeness of the stockpile. A protocol for a stockpile and decision-making should include criteria for triage and setting priorities for allocation and distribution in cases of limited availability of medical products.

**Personnel and training**

A variety of specialist skills are necessary to establish a stockpile, including health-care providers trained in radiation medicine and/or emergency medicine, laboratory specialists, pharmacists, emergency response coordinators, logisticians and communications experts. In addition, specialists will be required to maintain and calibrate equipment and devices which might be also included in the stockpile. Regular training should be provided to develop and update the skills of all relevant personnel involved in emergency operations for understanding the processes and protocols of maintenance and use of emergency stockpiles.

**Communication**

A communications strategy that includes key messages and various information products for the public and specialists is necessary to ensure proper use of a stockpile. Public communications might include explanation of the criteria for prioritizing access to the stockpile and special considerations for vulnerable groups, such as children and pregnant and lactating women.

An information toolkit for stockpile users might be useful. It could include fact sheets for different types of emergencies, casualty management, medical treatment with elements of the stockpile, protocols, guides, procedures and current guidelines for medical management in the country. Specialists involved in decision-making and use of the stockpile should have access to this information and the necessary education and training.

**5.2 Roles of stakeholders and organizations**

Examples of support from the international community in responses to health emergencies, disease outbreaks, natural disasters and military conflicts include a long list of international stakeholders that provide humanitarian assistance, ranging from large intergovernmental entities (e.g., specialized agencies of the United Nations system) to small nongovernmental organizations and charitable foundations. This section is limited to the description of the roles of national stakeholders and WHO, although many other stakeholders and international partners offering support and humanitarian assistance will play an important role as well.

**National stakeholders**

National stakeholders include national and local health authorities, health-care facilities, pharmaceutical suppliers, civil defence and emergency services, etc. Each stakeholder may have specific responsibilities pertaining to their mandates and roles in the response. These responsibilities range from putting in place enabling tools and mechanisms (e.g., appropriate national legislation and mechanism for licensing and approval of medical products) to practical arrangements for the use of stockpiles (e.g., acquisition,
maintenance, storage, transport, deployment, replenishment, monitoring and evaluation). Relevant legislation, rules and procedures are required to facilitate and coordinate these processes. Coordination among local, regional and national emergency responders and stockpile managers is crucial for timely, efficient use of the stockpile. Ensuring access to necessary communication tools and training for relevant personnel is an important part of the national stakeholders mandate.

WHO

WHO monitors Member States’ preparedness for health emergencies, including radio-nuclear hazards (1), and provides policy advice and technical assistance on matters pertaining to public health and clinical interventions in radiological and nuclear emergencies. Assistance may be provided in the area of strengthening health sector’s preparedness for radiation emergency, provision of technical guidance and policies, capacity-building and development of a radiation emergency stockpile, reviewing its formulary, or making a recommendation on sharing of the stockpile between countries or within regions to optimize the local public health response. As a global leader in public health, WHO facilitates the delivery and sharing of medical supplies among its Member States and also facilitates their procurement and provision during health emergencies (e.g., vaccines, antibiotics, antivirals, parenteral solutions, personal protective equipment, trauma and survival kits), with services and equipment (such as information technology and communications, rapid transport vehicles and ventilators) (78). While all decisions on public health interventions are made by national health authorities, in a health emergency WHO may make recommendations regarding public health response and case management, and may also facilitate transfer or repatriation of a patient to a country in which the necessary services are available, if required.

In advising Member States, WHO uses its expert networks and collaborating centres, including the Radiation Emergency Medical Preparedness and Assistance Network (REMPAN), which links agencies and specialists with expertise and experience in public health preparedness and response to a radiation emergency (79). In response to a request for medical or public health assistance, REMPAN experts may be contacted to support WHO’s response to health emergencies, disasters and humanitarian crises involving radio-nuclear hazards and risks.

WHO is a member of the Inter-Agency Committee on Radiological and Nuclear Emergencies (IACRNE) (80), consisting of some 20 international organizations. IACRNE provides a mechanism for coordinating international arrangements for preparedness and response under the leadership of the International Atomic Energy Agency (IAEA) (81). In case of an emergency, WHO liaises with the IAEA to verify an emergency report, to obtain further information on the extent and scope of the emergency and potential risks it may represent to human health and the environment. Through secure communication channels IAEA informs IACRNE members and its member states on the emergency status updates and prognosis, on the meteorological situation and implications for transport and trade and other relevant information. IACRNE member organizations, in line with their respective mandates, will coordinate their actions and provide consistent advice to their respective member states with regard to the urgent protective actions outlined in international safety standards and guides (82).
5.3 Concept of operations

Development of a concept of operations is vital for managing a stockpile. It is elaborated collaboratively by the stakeholders involved in emergency response and approved by the national authorities. A concept of operations describes the conditions under which a stockpile would be used, the overall strategy and goals for its use, how it is managed and maintained and the process by which international assistance may be requested.

**Creating the stockpile:** The concept of operations should provide details for setting up the stockpile, including:

- the scope, structure and size of the stockpile according to operational assumptions;
- purchase and contract management (including rotation of supplies, assistance in emergencies, quality assurance and a vendor-managed inventory for surge demands); and
- selection of locations and facilities for the stockpile according to resources, safety considerations and security requirements.

**Managing the stockpile:** The concept of operations should provide detailed information for:

- inventory management, including periodic review, quality assurance, quality control, evaluation and updating of the inventory; storage conditions, tracking, maintenance and rotation of the inventory; and replenishment after emergency use;
- emergency protocols, including the mechanism of communication, detailed information (who, when, how) on requests for use of the stockpile and the steps for approval of the request, deployment and implementation;
- staffing requirements, including the team composition and professional qualifications, roles and responsibilities, and training of the field team that will be deployed in an emergency;
- integration of the procedures for stockpile use into overall local, regional and international emergency response plans; and
- provision of the necessary training to the field teams that will be deployed in an emergency and to medical specialists who will manage cases of radiation injuries.
5.4 Cost, source of supplies, commitment of resources and management

Establishing a national stockpile may incur a substantial initial cost, while maintaining it requires reliable, sustainable sources of pharmaceuticals, supplies and equipment and committed financial and human resources. The elements listed below should be carefully considered when planning a national stockpile of MCM and medical supplies for clinical management of radiation injuries.

**Cost:**
- purchase of pharmaceuticals, supplies and equipment;
- establishment and operation of an inventory management system for tracking, maintaining and rotating the inventory to prevent expiration;
- transport and storage of pharmaceuticals, supplies and equipment;
- staffing and associated training, including participation in emergency exercises; and
- replenishment of the stockpile after either expiry or use in an emergency.

**Source of supplies:**
- identification and evaluation of multiple sources of supply for pharmaceuticals, supplies and equipment;
- purchase agreements and arrangements for assistance during an emergency, rotation of products in the stockpile and possible provision of storage and a warehouse;
- contingency plans for potential problems such as supply failure, a manufacturer moving or production faults and mechanisms for preventing them; and
- possible use of a vendor-managed inventory for events that require additional surge demand for pharmaceuticals, supplies and equipment.

**Resource commitment and management:**
- initial resource commitment for purchase of pharmaceuticals, supplies and equipment; for preparation of warehouse facilities; for staffing and training; and for development and operation of the inventory management system; and
- continuing resource commitment for stockpile rotation, system maintenance, facility operation, retention of staff and expertise and participation in emergency exercises.

Countries and organizations have taken various approaches to developing and managing a stockpile of medical supplies. Annex 1 describes practices adopted by some countries. These examples should be used for reference only, as each national stockpile programme is tailored to the country’s particular needs and conditions.
5.5 Approaches to managing a stockpile

Various approaches have been used for stockpile management and access.

**Physical inventory**

A physical inventory is one that offers supplies in various ways, including:

- purchase of products to be stored in the warehouses of a strategic national stockpile and removed from the stockpile when they expire unless they are modified to exceed their original expiration dates within a shelf-life extension programme. A number of radiation-emergency stockpile products (e.g., decorporation agents) are maintained in this way (83). Smaller, operational stocks of essential pharmaceuticals (“tactical stockpiles”) can be made available at key health facilities to ensure early access for a few days, until the strategic stockpile supply is delivered.

- repurposing of some products for management of radiation injuries, which allows maintenance of excess products on the commercial market, with the advantage of significant savings in development and procurement;

- a vendor-managed inventory, which allows a product to be stored on a vendor’s site, where it is routinely rotated to avoid expiry (84); and

- a user-managed inventory “stock bubble”, which is a strategy used, for example in the USA, for access to myeloid cytokines approved for haematopoietic acute radiation syndrome. In such a system (also referred to as “forward deployment”), a product is stored at a hospital, pharmacy or aboard an emergency vehicle (85). This is an important, economical approach for drugs that must be delivered rapidly after irradiation and also offers a solution to the problem of drug expiration, which is important for high-cost, short-shelf-life cytokines (growth factors) used in haematology.

**Virtual inventory**

A virtual stockpile is an agreed quantity of a medical product set aside by the manufacturers or vendors for emergency allocation on request. Such a stockpile requires formal arrangements and procedures for requesting and deployment in an emergency. Experience with vaccine stockpiles shows that such approach may be feasible for certain medical products (5).

**Short-term loan**

A national stockpile may be developed as a reasonably small resource; however, a national stockpile may be depleted quickly in response to an emergency in which a large number of people need treatment, or the affected individuals require long-term treatment, and replenishing the supply may take time. This situation has been seen in many countries in the recent response to the COVID-19 pandemic. As radiological and nuclear emergencies are relatively rare and the drugs in the national stockpile must be replaced after their expiration dates, it would be unreasonable to advise establishment of a large national stockpile. Instead, establishing agreements with other countries to share medical products during an emergency could be a practical solution to assuring public safety. Such an arrangement may be envisioned as a “short-term loan”. Thus, in response to an emergency, one country can borrow products from the national stockpile of another country, with an agreement that the same quantity and quality of the drugs will be returned as soon as possible. For example, such agreements were developed between Canada and the USA and between Mexico and the USA in 2021, with bilateral agreements to allow 4 million doses of COVID-19 vaccine to be “lent” to Canada and to Mexico (86).
6.1 Investigational therapies

Basic and applied scientists are identifying new cellular and molecular pathways that can be exploited in novel treatments and are achieving technical advances that may result in new products for use during a radiation emergency. This section reviews emerging technologies and drug formulations, including potential repurposing of products previously approved for other indications.

**HOPO**

**Chemical name:** 3,4,3-(LI-1,2-hydroxypyridinononate), 3,4,3-(LI-1,2-HOPO)

**Indication:** Decorporation of radionuclides via complexation (comparable to DTPA)

HOPO is an experimental octadentate chelator (hydroxypyridinonate compound), which has been proven to be an effective, safe decorporating agent for actinides in rodents. HOPO can be given orally, is more potent than Ca DTPA and induced minor toxicity in a study in rodents (87). It has also been shown to decorporate Pu and Am from rodents even when given 5 days after exposure (88).

**Lung surfactants**

**Context:** Treatment of lung injury after exposure to radiation by inhalation

**Chemical name:** 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine, lucinactant
Indications: In addition to use of decorporating agents to remove radionuclides that have already reached the circulation, there is also interest in use of the lung surfactants that are in clinical use to eliminate particulate radionuclides that might lodge in the lung during inhalation. For example, lucinactant, a preventive therapeutic that is administered intratracheally to premature infants at risk of neonatal respiratory distress syndrome, has been studied for mitigation of radiation-induced lung injury. The drug preserved lung function (89) and significantly improved the survival of mice with radiation-induced lung injury (90).

Side-effects: The adverse reactions with this drug are related mainly to administration and include endotracheal tube reflux, pallor, endotracheal tube obstruction, oxygen desaturation and bradycardia, which may require interruption of dosing. Lucinactant should be administered only by or under the supervision of a clinician experienced in intubation and ventilator management. As the drug is used in neonatal respiratory distress syndrome (90), it may be used safely as a radiation MCM for both paediatric and adult populations.

Angiotensin-converting enzyme inhibitors

Context: Prevention and management of delayed effects of acute radiation exposure

Chemical names: 1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline; (2S)-1-[(2S)-6-amino-2-[(1S)-1-carboxy-3-phenylpropyl]amino]hexanoylpyrrolidine-2-carboxylic acid; (3S)-2-L-alanyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; captopril

Indications: Angiotensin-converting enzyme inhibitors are orally administered agents that are used routinely to treat hypertension and heart failure. They have also been shown to improve survival in several models of radiation injury, including studies in animals and humans in vivo (91, 92). Their mechanism of action in preclinical studies of delayed effects of acute radiation exposure of both the lung and the kidney suggests an effect apart from its anti-hypertensive effect (92). Widespread use of these inhibitors to treat high blood pressure has resulted in a wealth of data in paediatric, adult and elderly patients, and their effects on radiation injury appear to extend beyond their effect on blood pressure (93). Another benefit of these products is that they may dramatically increase survival, even when given weeks after exposure (92). Their efficacy has also been seen in humans given the drug after exposure to radiation. Analysis of data from a clinical trial showed that captopril reduced injuries to the kidney and lung in patients given a bone-marrow transplant after irradiation (94).

Side-effects: Common side-effects include headache, dizziness, hypotension, weakness, drowsiness, cough, diarrhoea and skin rash. Rare side-effects include abnormal taste sensation, hyperkalaemia, kidney failure and birth defects. (It should therefore, not be used in pregnancy.) Given its good safety profile, low cost, wide availability and potential off-label use for this class of drugs, angiotensin-converting enzyme inhibitors may be used in emergency settings in routine practice of medicine.

Erythropoiesis-stimulating agents

Context: Management of anaemia after exposure to ionizing radiation. The mechanism of action of erythropoiesis-stimulating agents suggests that they might be beneficial in people exposed to ionizing radiation, although no significant effect has yet been demonstrated.

Protein chemical formula: \( C_{815}H_{1317}N_{233}O_{241}S_5 \)

Indications: Erythropoiesis-stimulating agents have not been approved by the US Food and Drug Administration for use in radiological incidents. They have, however, been administered in combination
with other cytokines to people exposed to ionizing radiation (7). As they have not been administered as a single agent to people who have been irradiated, a global consensus made a weak recommendation for their use to avoid blood transfusions in people exposed to ionizing radiation resulting in or expected to result in haematopoietic injury (61). Preclinical data suggest that use of drugs that target erythroid progenitors and erythroid precursor cells may improve survival by contributing to recovery of erythropoiesis. This idea is supported by the results of studies in irradiated rodents administered exogenous erythropoietin and in nonhuman primates after administration of erythropoietin with other cytokines (95).

**Dosing:** Individuals exposed to ionizing radiation could be treated with an erythropoiesis-stimulating agent when the haemoglobin level is < 10 g/dL but only if the rate of decrease in haemoglobin would probably require transfusion of red blood cells. The goal is to reduce the risk of alloimmunization and other risks of red blood cell transfusion. The dose should be reduced or interrupted when the haemoglobin level is > 10 g/dL.

Administration of these agents is suggested by their use in patients with chronic kidney disease. The initial dose of epoetin-a is 50–100 units/kg body weight once weekly (96) or 10 000–20 000 units every other week (97). The initial dose of darbepoetin-a is 0.45 µg/kg once every 4 weeks, 0.45 µg/kg once a week or 0.75 µg/kg once every 2 weeks. Doses of < 1500 to ≥ 90 000 units of epoetin-a per week can be converted into doses of darbepoetin-a of 6.25–200 µg/week.

**Side-effects:** Therapy with erythropoiesis-stimulating agents may cause hypertension, headache and influenza-like signs and symptoms. Hypertension may be severe, leading to encephalopathy and seizures (98). The risk of hypertension can be reduced by adjusting the dose of erythropoiesis-stimulating factor to increase the haematocrit slowly to a target of 30–35%. Other side-effects, which occur in > 10% of cases, include oedema, abdominal pain, dyspnoea and cough.

### 6.2 Stem cell therapy and biobanking

Ionizing radiation alters stem and progenitor cell differentiation and proliferation, induces stem cell apoptosis and alters accessory cells and their products within the local microenvironment (99, 100). Tissue regeneration and subsequent recovery from radiation injury require that stem cells be radio-resistant in order to deal with these toxic effects (101, 102). After exposure that had severe effects on haematopoietic stem and progenitor cells, administration of allogeneic or unexposed autologous stem cells effectively mitigated haematopoietic injury after cytokine and supportive therapy had failed (103).

Use of stem cell transplantation therapy requires relevant legislation, rules and procedures to address the broad spectrum of issues relevant to the development of biobanks of human biospecimens (104). While biobanking is outside the scope of the current document, the two types of stem cell therapy are haematopoietic (Box 2 in section 4.3.1) and mesenchymal stem cell transplantation (Box 3).
The cutaneous response to ionizing radiation exposure is highly variable. It may resemble sunburn (for example, the beta burns observed after the Chernobyl NPP accident) or it may involve subcutaneous tissues, causing a severe musculocutaneous radiation syndrome (for example, accidental manipulation of a radioactive source for radiography at an industrial site). Both acute and chronic injuries include a neurovascular syndrome that induces severe, intractable pain. Traditional (thermal and electrical) burn management has been unsuccessful. Surgical excision with debridement of the necrotic tissue (skin, muscle and in some cases, bone resection) followed by skin grafts, dermal substitute grafts and, more recently, by flap rotation have been used with limited success. An innovative therapeutic strategy that combines classical surgery or skin allografts or autografts with the local mesenchymal stem cell transplantation has been used successfully during the past 20 years in a limited number of patients (16). This approach has relieved intractable pain and improved the quality of life of patients. The strategy requires an experienced plastic surgeon and access to cell therapy units.
Summary

A stockpile should reflect the national risk profile and must be of the appropriate size according to the scenarios for which the stockpile will probably be used. Typically, a national stockpile for radiation emergencies includes specific pharmaceuticals, PPE and special devices, while the scope of this publication is limited to the pharmaceuticals only.

The pharmaceutical elements of a stockpile for radiation emergencies are those medical supplies required in emergencies involving external and internal over-exposure to ionizing radiation to either prevent/reduce potential exposure or to manage health consequences of the exposure that has already occurred. They typically include KI tablets, decorporating agents, alkylating agents, cytokines and growth factors, antiemetics, anti-diarrhoeal agents and antimicrobial agents.

Good governance and management of a stockpile include formal regulations and procedures for maintenance, storage, packaging, release of stock and refurbishing. Stock control requires that pharmaceuticals and supplies be removed when their shelf-life is exceeded. Provision of a stockpile requires a financial commitment to maintain it for constant readiness and prompt restocking. A functional stockpile requires a concept of operations that describes the conditions under which the stockpile would be used and the overall strategy and goals for its use.

As the leading international organization in public health, with both the authority and responsibility to assist in radio-nuclear emergencies, WHO provides advice and guidance on stockpile development and may assist in procuring or sharing stockpile elements among countries. WHO's experience in establishing stockpiles of vaccines and other commodities and in sharing mechanisms can be used in setting up national stockpiles for radiation emergencies. WHO's global expert network REMPAN is an important asset of the Organization for implementing its work on providing technical guidance and tools for response, delivering activities for building capacity through education and training, and on promoting international cooperation and information-sharing between the members of the network and the professional community in the field of radiation emergency medicine.

Coordination of local, national and international responses is essential for a harmonized response to radiation emergencies. As a member of the IACRNE and the global leader of health, WHO provides advice and ensures access to medicines and health services for countries that are developing national capacity for preparedness and response to radiation emergencies.

Novel formulations of standard therapies, new therapeutics, repurposed drugs and formulations, stem cell therapies and emerging procedures for removal of internal contaminants will eventually become commercially available. They should be considered for future use in national stockpiles.
References


References


Annex - Examples of good practice in establishing and managing a national stockpile

The composition of a national stockpile for radiological and nuclear emergencies may be considered a matter of national security, and it may therefore, be difficult to collect the necessary information. This annex presents brief descriptions of the practices in several countries. The examples might be useful for other countries that are developing a national stockpile.

Practices in Argentina

The Nuclear Regulatory Authority maintains a permanent system for intervention in radiological and nuclear emergencies, which is operational 24h a day, with the participation of experts in dosimetry, environmental radiological impact, modelling and the medical response in radiological or nuclear emergencies. The national plan for responding to nuclear emergencies is being updated and integrated into the National System of Integral Risk and Disaster Management, created by Law 27287. Its objective is to establish specific policies and strategies for strengthening and optimizing actions to reduce risk and for crisis management and recovery.

The medical response is based on several framework cooperation agreements among the Nuclear Regulatory Authority and the national Ministry of Health, the Ministry of Health of the Autonomous Government of the City of Buenos Aires and the Secretariat of Civil Protection, under the Ministry of Security and the grassroots agencies that make up the National System of Integral Risk and Disaster Management.

Nuclear power plants and the Nuclear Regulatory Authority maintain a renewable (according to expiration date) basic stockpile of important blocking and chelating drugs, including KI, Ca DTPA, Zn DTPA and Prussian blue. The national stockpile comprises 107 500 KI tablets (130 mg), 1796 KI tablets (3.2 mg), 724 KI capsules (16.25 mg), 6480 Prussian blue units, 925 Ca DTPA ampoules, 720 Zn DTPA ampoules, 600 tablets of 2,3-bis(sulfanyl)propane-1-sulfonic acid and 250 ampoules of 2,3-bis(sulfanyl)propane-1-sulfonic acid.

Practices in Brazil

In 2014, the Brazilian Ministry of Health published a contingency plan for emergencies in public health due to chemical, biological, radiological and nuclear agents. The plan includes a list of medications established by the Ministry of Health as a national stockpile.

For nuclear emergencies, there is a stockpile of 200 000 KI tablets (130 mg) for the population at risk around an NPP located at Angra dos Reis, Rio de Janeiro State. The tablets are acquired by the Ministry of Health and stored by the local government. KI tablets are available at other NPPs according to the on-site nuclear emergency plan. Approximately 45 000 tablets are available for workers and their families who live...
near the plant and are pre-distributed to workers' families living within 3 km of the plant. Local stocks of Ca DTPA, Zn DTPA and Prussian blue are also available for prompt administration in case of an accident involving workers or emergency responders.

**Practices in France**

Decisions to acquire or renew strategic stockpiles are made by the Ministry of Health. An annual acquisition plan for a strategic national stockpile, which includes nuclear energy risks, is sent to the pharmaceutical department of the National Agency for Public Health (Santé publique France), which ensures the stockpile management. The acquisition plan indicates renewal of stocks and the target to be reached. The size of the stock is therefore, regularly updated. The acquisition plan also includes renewal of stocks and the target levels.

The response to a nuclear accident includes the following:

- information campaigns and free distribution of KI tablets (for prevention) are organized for local residents and public establishments in a 20-km radius around NPPs;
- reserve stocks of KI are available in all departments for rapid mobilization; and
- a secondary security stock of KI is available on Santé publique France platforms to refill departmental stocks as necessary.

To respond to a risk of internal contamination, there are “strategic” stockpiles of Ca DTPA and Prussian blue on national and regional platforms. In addition, local “tactical” stockpiles are located in hospital emergency units and in mobile emergency and resuscitation units to cover early response until strategic stocks can be mobilized.

**Practices in Germany**

Medical supplies are stockpiled at various levels, depending on the threat. For radio-nuclear events, stockpiles are generally regulated by law and procured at Federal level by the Federal Office for Radiation Protection, while the states store and distribute stocks. The law includes stockpiling of drugs that inhibit the uptake of radioactive iodine into the thyroid gland or of other radionuclides into the body, as well as decorporation agents. Currently, there is a stockpile of nearly 190 million KI tablets (65 mg) to cover the whole population for whom treatment is feasible; four tablets are distributed per person in case of an emergency.

Stockpiling of general medical supplies for mass casualty incidents, including chemical and biological events, is the responsibility of the State. Besides the “classic” stockpile (e.g., wound dressings, surgical consumables, analgesics), some antidotes for larger chemical events are included. Furthermore, every hospital pharmacy is committed by law to store at a minimum the average requirements for 2 weeks in cases of temporary shortages or greater demand.

A stockpile for national defence has been developed at Federal level, including emergency medical consumables and some pharmaceuticals. Products are stored in packages sufficient to treat 250 patients (40% type 1, red; 20% type 2, yellow; 40% type 3, green), located at several hospitals to ensure proper distribution. The list is published, and the latest version can be accessed online from the Federal Office for Civil Protection and Disaster Assistance.
Practices in Japan

To provide medical response in case of radiological or nuclear emergencies, five centres for advanced radiation emergency medicine are established throughout all regions of Japan.

The National Institute for Quantum Science and Technology is the leading Government institution and is the centre for Japan’s national stockpile of decorporation agents. The Institute developed a master plan for stockpiles of Ca DTPA, Zn DTPA and Prussian blue after discussions with the other four domestic centres and purchases these MCM with support from the national budget. The plan ensures that a critical volume of MCM is maintained in the stockpile, within the constraints of manufacturing and expiration dates.

In the past, only the National Institute for Quantum Science and Technology maintained a stockpile. As prompt administration in the event of actinide contamination is recommended, stockpiles are also maintained at four additional centres for rapid use in a radiation emergency.

Practices in the Republic of Korea

National stockpiles have been developed of KI and three types of decorporating agent (Ca DTPA, Zn DTPA and Prussian blue), which are purchased from the national budget for radiological disaster response. KI tablets are stockpiled in 130-mg and 32.5-mg doses for accurate dosing according to age. The stockpiles are managed by local governments for distribution to residents within a 30-km radius of an NPP. Currently, KI tablets are available for both urgent distribution in an emergency and for pre-distribution, according to a revision of the Act on Physical Protection and Radiological Emergency. In addition, KI and decorporation agents are stockpiled and managed by the WHO Collaborating Centre at the Korea Institute of Radiological and Medical Sciences and 31 other designated medical facilities throughout the country for use in a radiological or nuclear emergency.

Practices in the Russian Federation

Protective measures for the population during radiation accidents are regulated by Federal law, a Decree of the President and a Decree of the Federal Government. The content of emergency stockpiles for the civil population is approved by the Government to ensure safety throughout storage and for rapid deployment.

Emergency stockpiles of radioprotection agents are located at emergency centres of the Federal Medical and Biological Agency to serve the nuclear industry and enterprises that use radioactive materials. A formulary has been developed, and reserves of medicinal products are inventoried and stored in individual kits for prophylaxis and first aid for NPP workers and emergency responders. The radiation emergency kit contains Indralin (150 mg, 6 tablets) for emergency protection in the event of external radiation exposure; Ondansetron (4 mg, 4 tablets); KI (125 mg, 1 tablet); Prussian blue (Ferrocin, 500 mg, 2 tablets); and individual incident packages containing a decontamination agent to remove chemicals and radionuclides from the skin. The composition of radioprotective agents may be modified according to the technology of production, after approval by the medical organization that maintains production.
Practices in the USA

The US strategic national stockpile was initiated in 1999 and is currently overseen by the Office of the Assistant Secretary for Preparedness and Response. The Government has invested more than US$ 7 billion in medical products and works with vendors to ensure appropriate maintenance and planning for distribution in a public health emergency. Publicly available information on the holdings of the stockpile confirms that it contains products that could be used in a radiological or nuclear incident, including growth factors; antiemetics, including Ondansetron; analgesics; antimicrobial agents, including broad-spectrum antibiotics; antiviral agents, such as acyclovir; and antifungal agents. Products for other uses (e.g., burn and blast, fluid resuscitation and topical agents) are also stockpiled. Experts meet routinely to re-assess the items that should be available or should be removed from the repository. Clinical guidelines published in 2004 indicate that the units of medicines that might be required after a nuclear detonation of 1-kT or 10-kT can be extrapolated from the projected number of casualties.

The Government has identified four phases of the public health and medical response to a radiological or nuclear incident: from before the incident occurs (e.g., advance preparation and planning) to activities in the immediate aftermath (within 24 h) and weeks to months after the detonation (early and sustained response and recovery). It is anticipated that normal operations within an affected region could be affected for years. Guidance for each phase includes steps for each of three response sectors according to the nature of the response: general readiness, emergency medical care and delivery systems and resilience and recovery. The actions within each sector are further categorized into education, preparation, information, activation and communication. A detailed discussion of the US Nuclear Incident Medical Enterprise has been published. Activities related to the national stockpile are included in all four phases of response. Preparatory actions include deciding what to stockpile and how to address any disruption in vendor access, sharing resource within local and regional areas (including medical facilities) and planning how products will be received and distributed from the stockpile. During an actual event, the focus shifts to verifying that sites can receive products and ensuring that vendor-managed inventories are sent to the sites in greatest need. Later stages of response include consideration of staffing of the stockpile, resource shortages and the requirement for updated contracts for the federal stockpile response; and in the weeks after the incident, evaluating the levels of supplies in the stockpile and what requires replenishment.