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NERIS

Development of national stockpiles for radiation emergencies

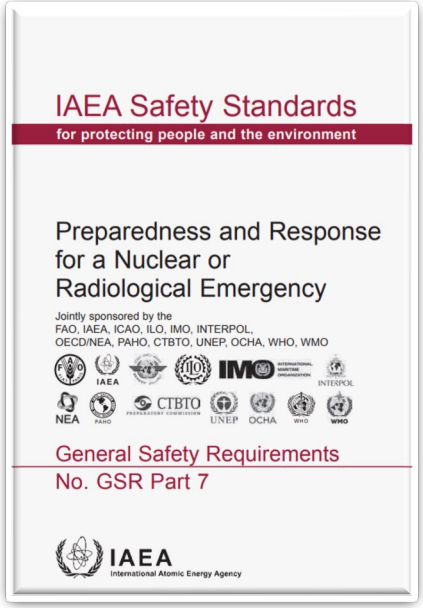
Dr. Zhanat Kenbayeva
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11.11.2024 – Rome, Italy

Why the Stockpile Policy Advice?

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GSR Part 7, Requirement N 12 on Managing the medical response in a nuclear or radiological emergency states:

The government shall ensure that arrangements are in place for the provision of appropriate medical screening and triage, medical treatment and longer term medical actions for those people who could be affected in a nuclear or radiological emergency



Stockpile Policy Advice development

- The first report on national stockpiles for radiation emergencies was a summary of a WHO Consultation held in 2007.
- Since then, new drugs came to market and were approved in several countries, new experiences emerged from managing and use of stockpiles health emergencies and new guidelines were developed.
- In 2021, a REMPAN Working Group (WG) was set up to revise the 2007 report and held five on-line meetings to develop the draft.
- Peer-review conducted in the 1st half of 2022.
- Feedback processed and document was finalized, edited and processed through WHO's publishing protocol by end 2022
- Published in Jan 2023

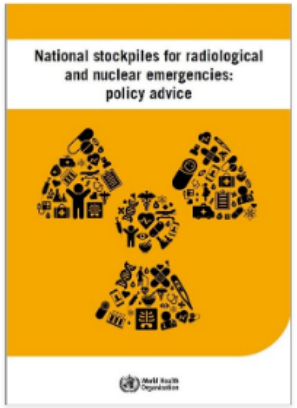


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URL: https://www.who.int/publications/i/item/9789240067875

National stockpiles for radiological and nuclear emergencies: policy advice

27 January 2023 | Policy brief



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Overview

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, and includes updated information on some of the pharmaceutical elements of stockpiles and additional information on medicines recently approved in recent years 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.

Read more

Radiation emergencies

Radiation and health

Strengthening global preparedness to radiation emergencies

REMPAN Radiation Emergenc Medical Preparedness and assistance network

News story

WHO updates critical medicines list for radiological and nuclear emergencies

WHO TEAM
Radiation and health

EDITORS
World Health Organization

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The structure of the document

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1. Introduction
1.1 Background
1.2 Scope
1.3 Target audience
1.4 Contributors to the advice
1.5 Management of conflicts or interests
1.6 Methodology for content development

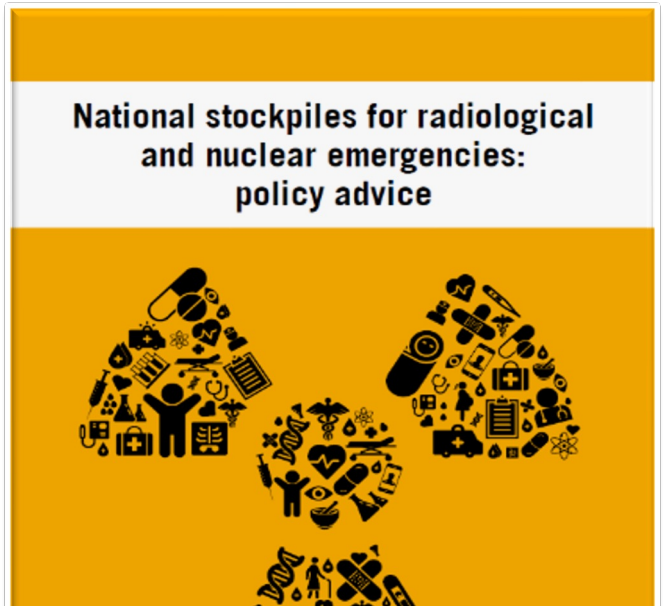
2. Health effects of radiation

3. National stockpiles: where to start?
3.1 Scenarios to be considered
3.2 Size of the stockpile

4. Stockpile formulary
4.1. Elements of a stockpile for radiation emergency
4.2 Internal contamination
4.3 Acute radiation syndrome

5. Stockpile management
5.1 Governance and management of a generic stockpile
5.2 Roles of stakeholders and organizations
5.3 Concept of operations
5.4 Cost, source of supplies, commitment of resources and management
5.5 Approaches to managing a stockpile

6. Research on medical countermeasures for clinical management of radiation injuries
6.1 Investigational therapies
6.2 Stem cell therapy and biobanking



Annex - Examples of good practice in establishing and managing a national stockpile
Practices in Argentina
Practices in Brazil
Practices in France
Practices in Germany
Practices in Japan
Practices in the Republic of Korea
Practices in the Russian Federation
Practices in the USA

1. Introduction



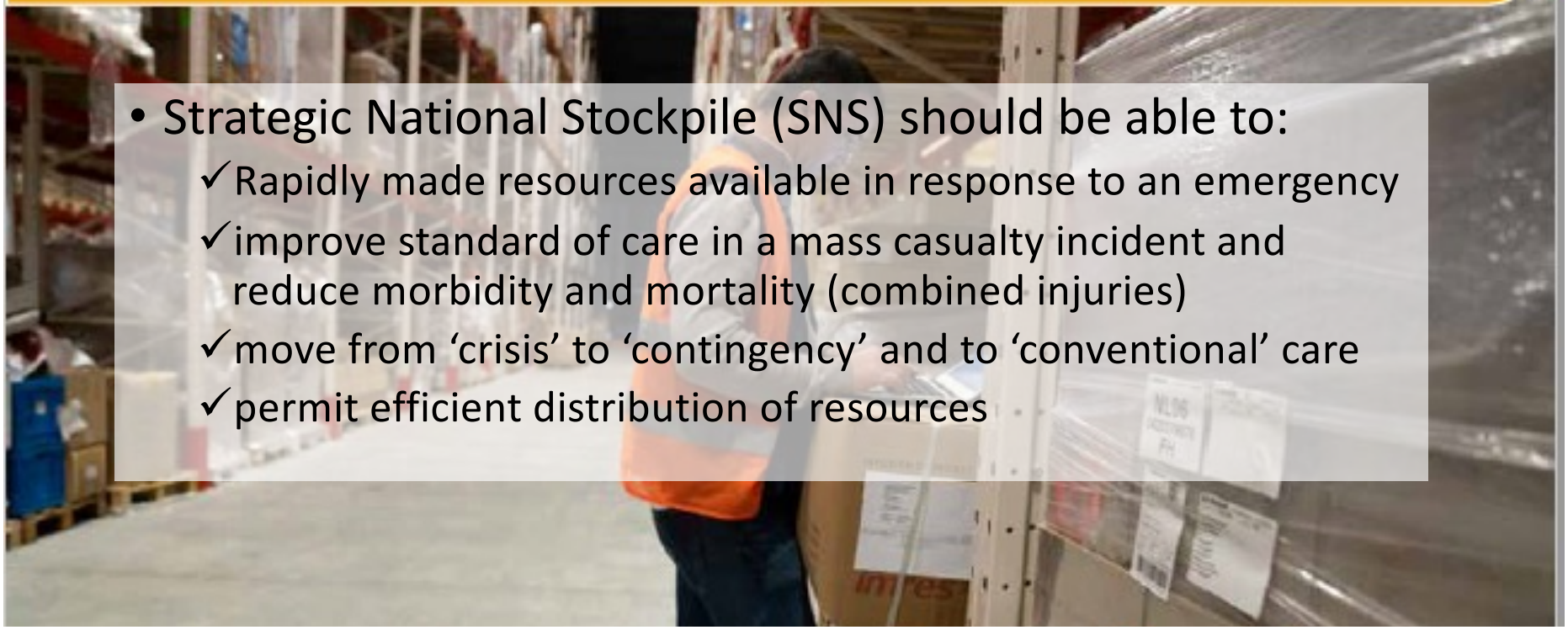
Target audience:

Public health administrators, policy makers, healthcare providers, and any other health professionals responsible for radiation emergencies preparedness and response.

2. Health effects of radiation



3. National stockpiles: where to start?



- Strategic National Stockpile (SNS) should be able to:
  - ✓Rapidly made resources available in response to an emergency
  - ✓improve standard of care in a mass casualty incident and reduce morbidity and mortality (combined injuries)
  - ✓move from ‘crisis’ to ‘contingency’ and to ‘conventional’ care
  - ✓permit efficient distribution of resources

Where to start?
Assumptions and Scenarios

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Decision to create a SNS requires

- understanding potential scenarios and types of radioactive sources that may be involved
  - Medical therapy (diagnostic imaging, brachytherapy and RT for cancer, etc.): ^{99}Tc, ^{82}Rb, ^{201}Tl, ^{82}Sr, ^{99}Mo, ^{60}Co, ^{137}Cs, ^{192}Ir, x-rays
  - Research : ^{32}P, ^{3}H, ^{14}C, ^{68}Ge, ^{90}Y, ^{86}Y, ^{194}Ir, ^{125}I, ^{123}I, ^{51}Cr, ^{67}Cu, ^{198}Au
  - Energy production (nuclear power plants [NPPs]): ^{235}U, ^{131}I, ^{137}Cs, secondary radionuclides
  - Industry (industrial radiography – gas/oil pipe fitting, metal welding, aircraft; RTGs; sterilized food; ceramics): ^{192}Ir, ^{90}Sr, ^{60}Co, ^{137}C, ^{59}Co
- Understanding threats (terrorists, states)
- Estimating the risk of each emergency scenario, as well as vulnerabilities
- Identifying the scope and elements of a SNS based on the information above

Where to start?
Assumptions and Scenarios

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Mass casualties from a nuclear detonation

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

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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.

Waselenko JK, MacVittie TJ, Blakely WF, Pesik N, Wiley ALL, Dickerson WE, Tsu H, Confer DL, Coleman CN, Seed T, Lowry P, Armitage JO, Dainiak N
Ann Intern Med 2004; 140 (12):1037-51.

Where to start?
Assumptions and Scenarios

- Sizing the SNS is determined by:
  - ✓ Scenario-based modeling:
    - Type of the scenario and specific radionuclides
    - Demographics (population size, age structure, niche density, mobility)
    - Socio-geographics (urban/rural, spatial variation in relation to terrain, transportation routes)
    - Health care delivery systems
    - Infrastructure (population transportation systems, communications, internet, public buildings, energy production- nuclear and hydroelectric power, oil and water transport)
  - ✓ Anticipated number of casualties based on likely scenarios
  - ✓ Distribution of injuries requiring emergent, urgent and long-term therapy
  - ✓ Dosing schedule and treatment duration for specific radiation countermeasures

4. Stockpile formulary



Internal contamination: Blocking and decorporating agents

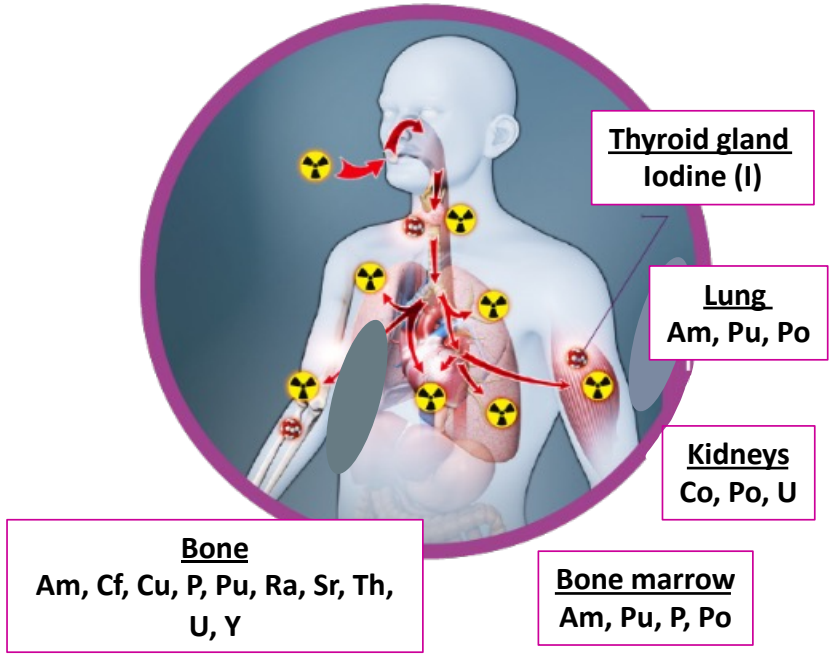
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Exposure routes

- Inhalation, ingestion, contaminated wounds

Therapy options

- Blocking agent (WHO 2017 guidelines on ITB in case of a nuclear emergency)
- Decorporating therapy (IAEA 2018 manual on internal contamination with RN):
  - Increases body excretion
  - Reduced RN distribution and retention in the target tissues/organs
  - Decreases chemical/radiological toxicity



Internal contamination: Blocking and decorporating agents

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- Blocking agent

Chemical name	Potassium iodide, KI
EML* 2021	Included for other indications
Indication	Prevention of accumulation of radioactive iodine isotopes
Route of application	Oral (breakable tablets; gel or liquid for children in some countries)
Dosing	130 mg KI (100 mg iodide) for people > 12 years and peidatric dosage
Shelf-life	Usually 5 years, with possible extension

** : WHO List of Essential Medicine*

- Decorporating agent

Chemical name	Ferric ferrocyanide (Prussian Blue), $Fe^{III}_4[Fe^{II}(CN)_6]_3$ x HO
EML 2021	Potassium ferric hexacyanoferrate is included for other indications
Indication	Incorporation of radioactive Cs isotopes, Tl intoxication
Route of application	Oral, 500-mg capsules of tablets
Dosing	Usually 3 x 1 g/day for 30 – 90 days
Shelf-life	Usually 5 years, shelf – life extension technically possible

Internal contamination: Blocking and decorporating agents

- Chelating agent

Chemical name	Ca- or Zn- Diethylene Triamine Penta Acetate, $CaNa_3$ DTPA : Ca DTPA, $ZnNa_3$ DTPA : Zn DTPA
EML 2021	Not included
Indication	Decorporation of transuranium elements or other polyvalent cationic elements
Route of application	Typically intravenous infusion, inhalation (for decorporation of inhaled radionuclides) and topical application (for wound decontamination). Oral formulations have been studied but were shown to be insufficiently effective.
Dosing	1 g daily for 5 days, 2-3 injections per week for 6 weeks followed by a break, total duration depending on the response
Shelf-life	5 years for sterile product when stored at 15 – 30 °C

Internal contamination: Blocking and decorporating agents

- Chelating agent

Chemical name	Aluminium phosphate, $AlPO_4$, sodium alginate
EML 2021	Not included
Indication	Ingestion of radioactive Sr
Route of application	Oral
Dosing	100 mL aluminium phosphate gel or 10 g sodium alginate
Shelf-life	Suspensions of aluminium phosphate: 3 years; suspension of alginate : 2 years

Chemical name	Sodium hydrogen carbonate, $NaHCO_3$
EML 2021	Included for parental use in other indications
Indication	Internalization of radioactive U
Route of application	Intravenous infusion, oral
Dosing	Intravenous : max. 1.5 mmol/kg body weight per h; oral : 2 tablets (1.0 – 1.3 g) every 4h
Shelf-life	Intravenous: 2 years; tablets: 3 years

External exposure to ionizing radiation

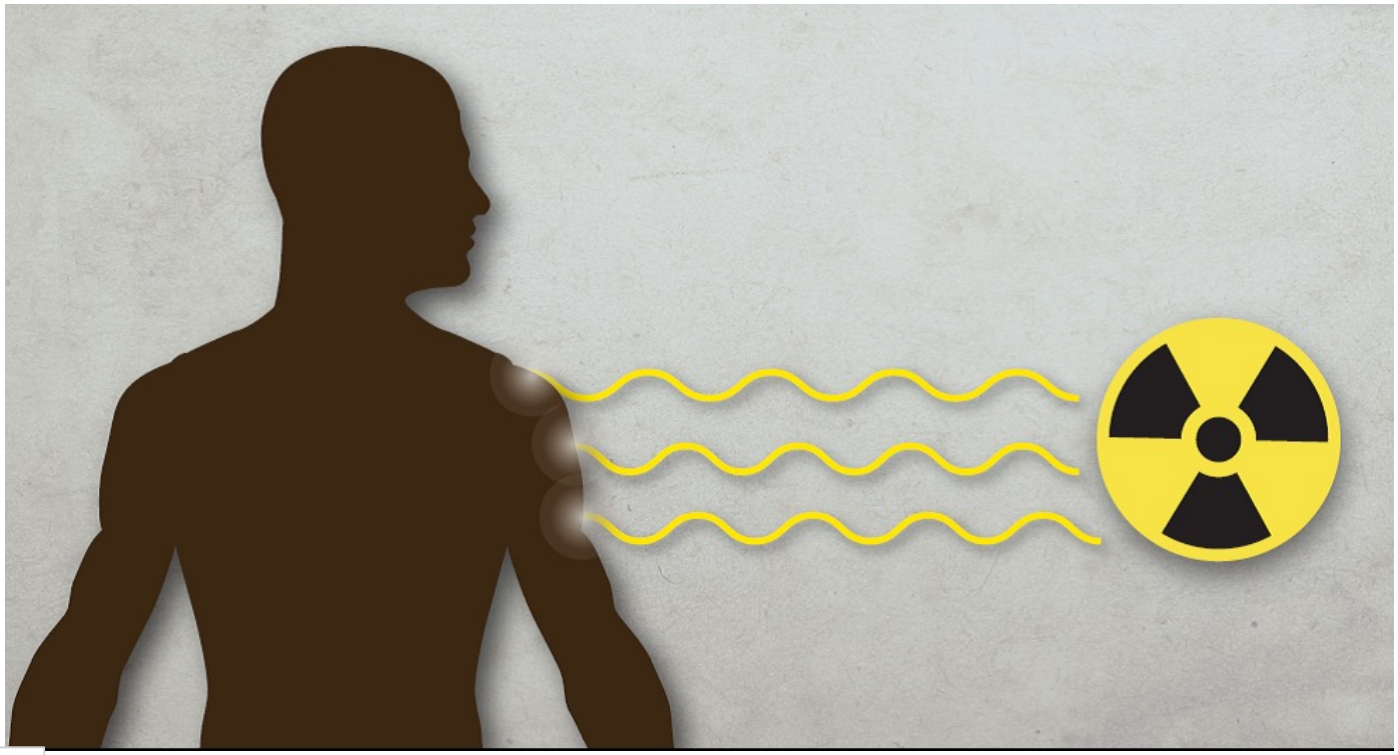


Image credit: US CDC website

External exposure: management of acute radiation syndrome

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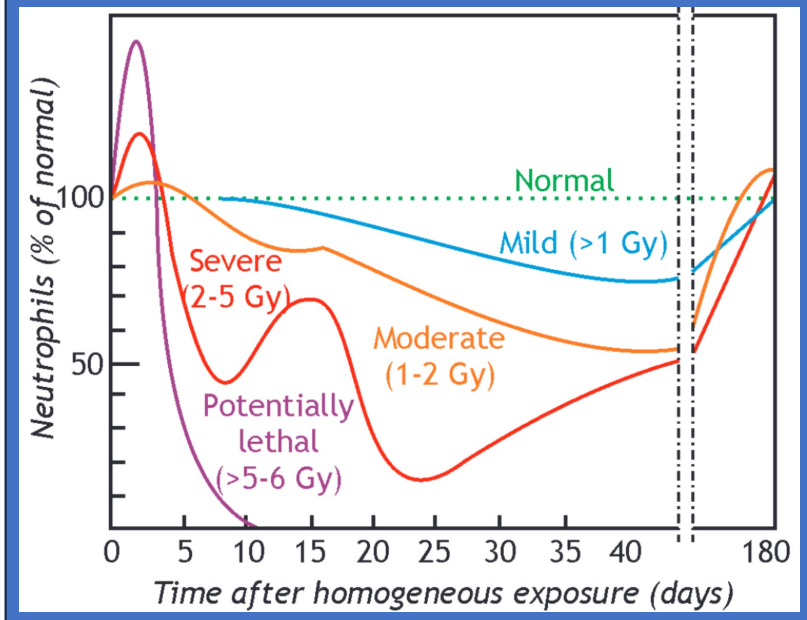
Exposure to a high dose of ionizing radiation may result in a life-threatening condition

Acute Radiation Syndrome (ARS)

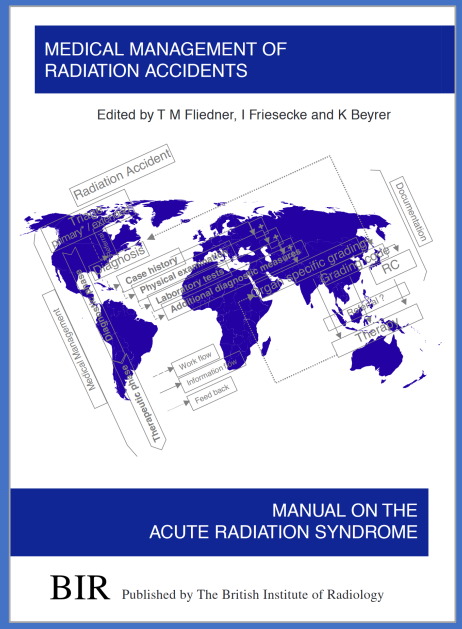
ARS manifestations (subsyndromes)

- hematopoietic
- gastrointestinal

(excluded cardiovascular and neurological)



https://www.ebmt.org/sites/default/files/2018-03/EBMT%20Nuclear%20Accident%20Committee%20Pocket%20Guide%202017.pdf



Fliedner TM, Friesecke I, Beyrer K. Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome. (METREPOL) published by Oxford: British Institute of Radiology; 2001)

External exposure: management of acute radiation syndrome

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Agents for the management of haematopoietic injury

Clinical evidence about the use of cytokines (in ARS) is limited. No clinical trials are available in humans regarding the treatment of ARS for obvious reasons.

Decision on inclusion of a specific agent (especially for cytokines) in the stockpile formulary was based on consensus of the working group experts and the outcome of peer review, including:

Evidence from

- large animal studies (leading to approval in 1 country)
- Case reports from individual patients treatments
- Data from use of the agent for other that ARS purposes, e.g., hematological patients and healthy volunteers

Drug	Country						
	Canada	Germany	France	United Kingdom	Japan	Russian Federation	USA
⋮							
(Peg) Filgrastim (G-CSF)	o	o	o	o	o	o	+
Sargramostim/Molgramostim (GM-CSF)	–	–	–	–	o	–	+
Romiplostim	o	o	o	o	o	o	+

+	Approved as MCM for radionuclide incorporation or radiation injury-related indication (on-label)
(+)	Approved but discontinued (e.g., by manufacturer)
o	Approved for other conditions not related to radionuclide incorporation or radiation injury (off-label)
-	No current approval

External exposure: management of acute radiation syndrome

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Agents considered for the management of haematopoietic injury

- growth factors (i.e., cytokines) targeting myeloid cells (granulocytes) (**G-CSF**) or granulocytes and macrophages (**GM-CSF**) enhance proliferation of progenitors, facilitate myeloid maturation, protect against apoptosis, and enhance cell function
- one growth factor to mitigate thrombocytopenia (**romiplostim**)
- one growth factor available to mitigate radiation-induced anaemia (although it is not approved for ARS)
- certain pharmaceutical products used to treat other clinical conditions that are also used in ARS management



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.

External exposure: management of acute radiation syndrome

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Agents for the management of haematopoietic injury

Granulocyte colony-stimulating factor (G-CSF)

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

- once daily, as soon as possible after a suspected or confirmed radiation dose of > 2 Gy
- huge experience in hematological and cancer patients, including healthy BM donors

Granulocyte–macrophage colony stimulating factor (GM-CSF)

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

- once daily, as soon as possible after a suspected or confirmed radiation dose of > 2 Gy

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

- first dose is administered as soon as possible after suspected or confirmed exposure to > 2 Gy
  second dose is administered 1 week after the first
- huge experience in hematological and cancer patients, including healthy BM donors

Romiplostim

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

- single dose as soon as possible after a suspected or confirmed radiation dose of > 2 Gy

External exposure: management of acute radiation syndrome

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Agents considered for management of gastrointestinal Injury

Whole-body exposure to ionizing radiation at doses ≥ 5 Gy induces breakdown of the GI barrier/tract leading to

- severe secretory diarrhoea and dehydration
- electrolyte imbalance
- invasion of enteric bacteria into the blood circulation

Today, there are no specific therapeutics approved by regulatory bodies for treatment of GI radiation injury.

Symptomatic treatment is limited to fluids and electrolytes, antiemetic compounds, anti-diarrhoeal drugs and antimicrobial agents

Ondansetron

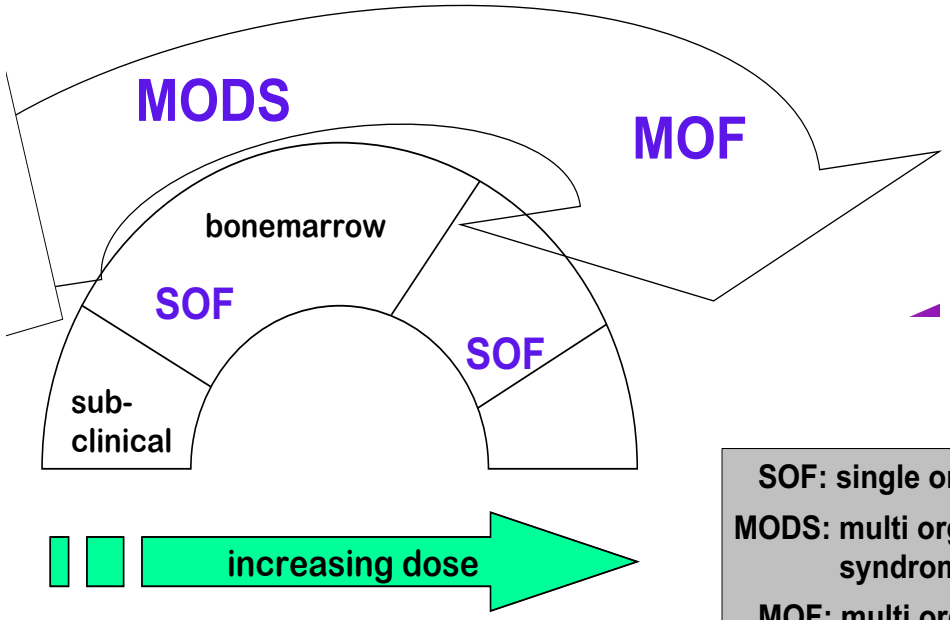
Chemical name	Ondansetron
EML 2021	Included
Indication	Antiemetic therapy
Route of application	Intravenous infusion, orally as melting tablets or film tablets
Dosing	Intravenous: 8 or 0.15 mg/kg body weight; oral: 8 mg once or twice daily
Shelf-life	Sterile intravenous and oral forms: 3 years

Loperamide

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

External exposure: management of acute radiation syndrome

Acute Radiation Syndrome is not a sum of isolated subsyndromes



SOF: single organ failure
MODS: multi organ distress syndrome
MOF: multi organ failure

No successful treatment was shown in patients with ARS on treatment with single agents only.

A combined effort including hospitalization at intensive care (with availability of laminar flow rooms) is necessary for a successful implementation of this stockpile.

This includes non-radiation specific drugs need to be stockpiled including

- **antibiotics**
- **antifungals**
- **Antivirals**

… and access to **blood products.**

5. Stockpile management



Stockpile Governance and Management

National emergency management plan should provide basis for SNS use

- National risk profile, assumptions and modeling results
- National preparedness capabilities and capacity

- Legal aspects of SNS management
  - Legislation on procurement (approval of medical products/devices)
- Decision-making protocols for releasing the SNS elements in emergency
  - Criteria for prioritizing allocation and distribution of the medical products
- Communication strategy
  - Timelines and priorities for access

Stockpile Governance and Management

Roles and Responsibilities:

- National stakeholders (health authorities, emergency response agencies, healthcare facilities, pharmaceutical suppliers etc)
- International organizations (WHO, IAEA, regional partners e.g. European Commission
- Neighboring countries through bilateral arrangements

Concept of Operations for a SNS:

- Setting up the stockpile (scoping and sizing, procurement, storage)
- Managing the stockpile (inventory, protocols for deployment, integration into the overall response plans, refill)
- Staffing and training

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Approaches to Managing a National Stockpile

- A physical inventory
  - Warehouse-stored inventories
  - Vendor-managed inventories
  - User-managed inventory (“stock bubble”)
- Virtual inventory
- Short-term loan



Stockpile Governance and Management

Resource Commitment and Management

- Substantial initial cost
  - Purchase of pharmaceuticals, supplies, equipment
  - Other cost
- Sustainable finance and human resources
  - Replenishment after use and stockpile rotation
  - Maintenance of facilities and expertise
- Reliable and sustainable sources of supplies
  - Purchase agreement, assistance during an emergency, contingency plans

6. Research on medical countermeasures for clinical management of radiation injuries



R & D for Medical Countermeasures Investigational Therapies to watch

- **HOPO -** Experimental oral drug that seems promising for an effective and safe decorporating agent for actinides and more potent than DTPAs (decorporates Pu & Am when given 5 days post-exposure)
- **Lung Surfactant - u**nder consideration for radiation-induced lung injuries (used for treatment of premature infants with respiratory distress syndrome), preserves lung function and improves survival in irradiated animals
- **Angiotensin Converting Enzyme (ACE) Inhibitors** (Lisinopril, Captopril, Enalapril, Fosinopril widely used for hypertension, heart failure, and other clinical conditions) show increased survival in rodents when dosed weeks post-irradiation, clinical trial showed reduced kidney and lung injuries in irradiated patients
- **Erythropoietin (EPO) Stimulating Agents** used for treatment of anemia associated with chronic renal failure and conditions, used off-label in radiation accident patients by promoting recovery of red blood cell production post-irradiation. In rodent studies showed a radiation survival benefit
- **Mesenchymal Stromal Cells (MSCs)** - innovative strategy for radiation skin burns combining classical surgery/skin grafts with local MSCs – used successfully in a limited number of patients

Thank you!

CarrZ@who.int



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