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Update to Current Policies for Use of Radiation Therapy Drugs

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Executive Summary

Potassium iodide (KI) and Prussian blue are medical countermeasures (MCMs) that are used to decrease the effects of internal radiological exposure. KI protects the thyroid against iodine-131 (^{131}I). ^{131}I is a product of nuclear fission and is most often encountered in nuclear reactor accidents. Prussian blue binds radioactive cesium or thallium. Cesium-137 (^{137}Cs) is a product of nuclear fission but is also associated with medical sources, radiological dispersion devices (RDDs), nuclear reactors, and nuclear weapons. Both ^{131}I and ^{137}Cs are beta particle and gamma ray emitters. The radiation from ^{131}I can induce thyroid cancer, especially in children, and the radiation from internal contamination with ^{137}Cs can cause a variety of cancers.

The Department of Defense (DOD) policies for KI and Prussian blue have not been updated since 2004 and 2005, respectively. Some additional research and some policy changes (in the U.S. and around the world) since that time could affect the utility of or scientific guidance underlying the DOD policies. This paper, written for the U.S. Army Office of the Surgeon General (OTSG), reviews the scientific literature and policies that have been published since 2004 to determine whether or why any changes to the current DOD policies are warranted and makes recommendations accordingly.

Most research published since the DOD policies were created reinforces the previously made policy decisions. While some policy changes have occurred since the original DOD policies were created, many of them were small or later reversed. However, some potential improvements to policy would ensure that the DOD policy is streamlined with the policies of the services and would better enable the DOD to promptly provide the proper doses of KI to children and to better maintain its current Prussian blue stockpiles. The potential changes to the DOD stockpiling of KI would be in addition to the current state guidance on which the DOD bases its stockpiling requirements.

Key recommendations to the DOD for updating policy or ensuring that the MCMs are properly distributed when needed are as follows:

- KI
  - Assess DOD stockpile of KI and potentially adjust stockpile to improve preparedness to provide KI to children.
    - For select areas and stockpiles, include 32-mg tablets or liquid doses of KI, which are necessary and more appropriate dosages for children, in addition to the currently stockpiled 130-mg tablets.

  - Ensure that stockpiles of KI are positioned within 10 miles of a nuclear power plant (either in the United States or outside the United States) so that those most likely to be affected can receive doses within four hours. Complying with this recommendation may require additional stockpiling at military bases, along with state stockpiles.

- Prussian Blue
  - Adjust DOD policy regarding dosing regimen to ensure it is consistent with current Army policy of 1 g three times daily for adults and then provide a definitive administration timeline.
  - Review and adjust the Prussian Blue stockpile to ensure that stocked amounts and storage conditions are appropriate.

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1. Introduction

A. Current Department of Defense (DOD) Policies

Potassium iodide (KI) and Prussian blue are medical countermeasures (MCMs) that are used to decrease the effects of internal radiological exposure. KI protects the thyroid against iodine-131 (^{131}I), which is a product of nuclear fission and is most often encountered in nuclear reactor accidents. Prussian blue binds radioactive cesium or thallium. Cesium-137 (^{137}Cs) is a product of nuclear fission but is also associated with medical sources, radiological dispersion devices (RDDs), nuclear reactors, and nuclear weapons. ^{131}I and ^{137}Cs are beta particle and gamma ray emitters.[1] Beta particles are radioactive particles can penetrate the skin but can be even more dangerous when ingested. Beta particles can damage tissue or deoxyribonucleic acid (DNA) either on the skin (external radiation) or throughout the body (internal radiation). Gamma rays are made of photons and can pass completely through the body, damaging tissue or DNA inside.[2] The radiation from ^{131}I can produce thyroid cancer, especially in children, and the radiation from internal contamination with ^{137}Cs can cause a variety of cancers.

The DOD policies for KI and Prussian blue have not been updated since 2004 and 2005, respectively. Thus, the risk is that patients treated with Prussian blue or KI will not receive medical care that is in sync with the last decade-plus of scientific research. Other associated policies, such as guidelines for the Strategic National Stockpile (SNS) or guidelines for the Federal Emergency Management Agency (FEMA), could have also changed in the interim. This paper, written for the U.S. Army Office of the Surgeon General (OTSG), reviews the scientific literature and policies that have been published since 2004 to determine whether or why any changes to the current DOD policies are warranted and makes recommendations accordingly.

B. Scope and Methods

To determine whether any changes to current DOD policy are warranted, we performed a qualitative literature review of policy, doctrine, and scientific literature. We primarily focused on papers or policies/doctrine published since 2004, although key literature

[1] "Radionuclide Basics: Iodine," United States Environmental Protection Agency (EPA), last updated May 28, 2019, accessed January 27, 2020, https://epa.gov/radiation/radionuclide-basics-iodine#self; "Radionuclide Basics: Cesium-137," United States Environmental Protection Agency (EPA), last updated May 4, 2017, accessed January 27, 2020, https://epa.gov/radiation/radionuclide-basics-cesium-137#self.

[2] "Radionuclide Basics: Cesium-137."

or policies from before that time were also reviewed to better understand the basis for the existing policies.

In addition to papers or policies specifically called out in current DOD policy, we performed searches on Google Scholar, ProQuest, the Army Publishing Directorate, and the Executive Services Directorate. In addition, we found current World Health Organization (WHO) and European Union (EU) policies in case they had been updated since 2004. Search terms included "Prussian blue" or "potassium iodide" + "treatment," "stockpile," "radiological," "nuclear," "medical," "toxicity," "policy," "side effects," or "dosing." Relevant references were taken from papers found in the initial searches. Papers not written in English were not reviewed.

Chapter 2 discusses current policy and scientific literature on KI. Chapter 3 discusses current policy and scientific literature on Prussian blue. Chapter 4 provides the conclusions of the analysis and recommendations for updates to policy.

2. Potassium Iodide (KI)

A. Introduction

^{131}I is a radioactive isotope of iodine that can be produced by nuclear reactor accidents and other releases of radioactive material.[3] Although radioactive iodine can be released during a nuclear attack, the level of radioactive iodine is generally low compared to other radioactive isotopes.[4] A correlation existed between the age at the time of the Hiroshima and Nagasaki attacks and the incidence of thyroid cancer,[5] although increases in thyroid cancer compared to other cancers were not observed after Hiroshima and Nagasaki nor after the Nevada atomic tests.[6] Instances of thyroid cancer increased in individuals on the Marshall Islands following the atomic bomb test on Bikini Atoll, possibly due to ingested iodine rather than inhaled iodine.[7]

When inhaled or ingested, ^{131}I can cause thyroid damage, especially in young children. Children are at higher risk of iodine-induced thyroid damage because their thyroids are more radiosensitive and concentrate more iodine compared to their body weight than adults do. Following the nuclear power plant accident at Chernobyl in 1986, 20,000 individuals younger than 18 years old at the time of the accident were diagnosed with thyroid cancer.[8] The increase in thyroid cancer was first discovered among Belarusian children in 1992.[9] The increase above baseline levels among children from the former USSR was more pronounced in the 5–10 years immediately following the accident, although the increase above baseline has persisted since that time.[10] Following the Fukushima Daiichi accident in 2011, no similar increase in thyroid cancer occurred among children. The Fukushima

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3 National Research Council, *Distribution and Administration of Potassium Iodide in the Event of a Nuclear Incident* (Washington, DC: National Academies Press, 2004), 2, https://doi.org/10.17226/10868.

4 Ibid., 48.

5 D. L. Preston et al., "Solid Cancer Incidence in Atomic Bomb Survivors: 1958–1998," *Radiation Research* 168, no. 1 (July 2007): 43, https://doi.org/10.1667/RR0763.1.

6 National Research Council, *Distribution and Administration of Potassium Iodide*, 48.

7 Ibid., 50.

8 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), "Evaluation of Data on Thyroid Cancer in Regions Affected by the Chernobyl Accident" (New York, NY: United Nations, 2018), v, https://www.unscear.org/docs/publications/2017/Chernobyl_WP_2017.pdf.

9 Vasili S. Kazakov, Evgeni P. Demidchik, and Larisa N. Astakhova, "Thyroid Cancer After Chernobyl," *Nature* 359, no. 6390 (September 3, 1992): 21, https://doi.org/10.1038/359021a0.

10 United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), "Evaluation of Data on Thyroid Cancer," 10–12.

Daiichi accident, however, released ten times less ^{131}I than the Chernobyl accident (see Subsection 2.D.2).

KI is an over-the-counter drug that saturates the thyroid with stable iodine,[11] preventing uptake of radioactive iodine and decreasing the risk of cancer following exposure. Because KI works as a preventive measure, it should be taken as soon as possible after exposure to radiation. When taken hours or days after the exposure, it can have diminishing effects. KI, as a salt, has a long shelf life. It does not prevent other forms of cancer beyond thyroid cancer. Since the risk of thyroid cancer from radioactive iodine decreases with age, KI is most effective in children.[12]

B. Current DOD Policy

The current DOD policy for KI (HA Policy 04-012; June 8, 2004) is based upon FEMA and Food and Drug Administration (FDA) guidance.[13] The FEMA guidance, published on January 10, 2002, states that "KI should be stockpiled and distributed to emergency workers and institutionalized persons for radiological emergencies at a nuclear power plant, and its use should be considered for the general public within the 10-mile emergency planning zone (EPZ) of a nuclear power plant. However, the decision on whether to use KI for the general public is left to the discretion of states and, in some cases, local governments."[14]. Although the FEMA guidance has not been updated since 2002, associated laws have since been updated and modified and are discussed in Subsection 2.C.1.

DOD policy states that military facilities located within the United States (should coordinate any distribution of KI with the state or local authorities if distribution is necessary.[15] For overseas bases, "all Geographic Combatant Commanders shall evaluate the threat of radioactive iodine release from CLBN [commercial land-based nuclear] power plants and develop plans to protect personnel and potentially use KI for appropriately selected personnel as a supplement to evacuation and sheltering."[16] Implementation should be consistent with the policy of the host nation or local government, where relevant.

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[11] National Research Council, *Distribution and Administration of Potassium Iodide*, 4.

[12] Ibid.

[13] William Winkenwerder, "Policy for the Use of Potassium Iodide for Protection of Service Personnel and Family Members," HA Policy 04-012 (Washington, DC: The Assistant Secretary of Defense, June 8, 2004), https://health.mil/Reference-Center/Policies/2004/06/08/Policy-for-the-Use-of-Potassium-Iodide-for-Protection-of-Service-Personnel-and-Family-Members.

[14] Federal Emergency Management Agency, "Federal Policy on Use of Potassium Iodide (KI)," *Federal Register* 67, no. 7 (January 10, 2002): 1356, https://www.fema.gov/media-library-data/20130726-1830-25045-9244/frn_v._67_n._7.pdf.

[15] Winkenwerder, "Policy for the Use of Potassium Iodide," 1.

[16] Ibid., 1–2.

The dosing guidance in DOD policy is taken from FDA policy on KI, which has not been updated since December 2001.[17] Most of the dosing guidance and understanding of adverse effects is taken from Chernobyl. Table 1 depicts the dosing instructions by age. Side effects of KI are minimal, so dosing as early as possible is recommended rather than determining an actual thyroid exposure beforehand. Risk of overdosing is also minimal compared to the benefits of potassium iodide.[18] The groups most likely to have side effects from KI are adults (who are less likely to benefit from potassium iodide anyway) and neonates (children under 1 month old). The benefits of KI still greatly outweigh the risks from KI for neonates, but neonates should be monitored for hypothyroidism after receiving KI. In order for infants to receive potassium iodide, the pills or a liquid solution of KI should be mixed with milk, formula, or water.[19]

Table 1. KI Dosing Guidelines

Threshold Thyroid Radioactive Exposures and Recommended Doses of KI for Different Risk Groups				
	Predicted Thyroid exposure(cGy)	KI dose (mg)	# of 130 mg tablets	# of 65 mg tablets
Adults over 40 yrs	≥500	130	1	2
Adults over 18 through 40 yrs	≥10			
Pregnant or lactating women	≥ 5			
Adoles. over 12 through 18 yrs*		65	1/2	1
Children over 3 through 12 yrs		32	1/4	1/2
Over 1 month through 3 years		16	1/8	1/4
Birth through 1 month				

*Adolescents approaching adult size (≥ 70 kg) should receive the full adult dose (130 mg).

Source: U.S. Department of Health and Human Services, "Guidance: Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies" (Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research, December 2001), 6, https://www.fda.gov/media/72510/download.

Note: The abbreviations in this table are defined in Appendix C of this paper.

[17] U.S. Department of Health and Human Services, "Guidance: Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies" (Rockville, MD: Food and Drug Administration Center for Drug Evaluation and Research, December 2001), https://www.fda.gov/media/72510/download.

[18] Ibid., 7.

[19] Ibid., 6.

KI protects the thyroid from radioactive iodide for approximately 24 hours. Therefore, individuals should take KI daily until they are no longer exposed to radioactive iodide. In most instances, however, within a day, individuals should be able to evacuate the contaminated area and/or avoid eating or drinking food and beverage that has been contaminated with ^{131}I.

C. Changes to U.S. and World Policy Since 2004

1. U.S. Policy

Most of the policies upon which the DOD policy relies have not been changed since the DOD policy was issued in 2004; however, the only major change that has occurred relates to stockpiling KI. Although the FEMA guidance on which the DOD policy is partially based has not been updated since January 2002, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (which the DOD policy does not discuss) was enacted in June of that year and changed the stockpiling procedures for potassium iodide.[20] That act states that "[t]hrough the national stockpile under section 121, the President, subject to subsections (b) and (c), shall make available to State and local governments potassium iodide tablets for stockpiling and for distribution as appropriate to public facilities, such as schools and hospitals, in quantities sufficient to provide adequate protection for the population within 20 miles of a nuclear power plant."[21] Thus, the Act changed the stockpile to include doses for those within 20 miles of the nuclear power plant rather than 10 miles, as before.

In addition to changing the radius for the stockpiling requirement, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 states that the President was to establish guidelines for stockpiling and distributing KI within a year of the act. A National Academies study was performed to assess the current condition of stockpiling across the states and the best method of distribution.[22] KI distribution and stockpiling is governed at the state level rather than the federal level. The National Academies noted a wide range in the state level stockpiling and distribution of KI.[23] It noted that distribution should be included in planning for radiological incident response and also that most stockpiles only included 130-mg tablets, which is the recommended dose for adults. Most stockpiles did not include any smaller doses for children, especially the 32-mg doses for children 1 month to 3 years old or liquid doses for infants.[24] Stockpiling 32-mg doses could

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[20] Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, 116 Stat. 594 (2002), SEC. 127, https://www.energy.gov/sites/prod/files/2014/03/f12/PL107-188.pdf.

[21] Ibid., 116 Stat. 615.

[22] National Research Council, *Distribution and Administration of Potassium Iodide*.

[23] Ibid., 127–133.

[24] Ibid., 26.

allow for easier dosing of children, the group most likely to benefit from KI.[25] In addition, Naval nuclear reactors were determined not to be of concern for stockpiling.[26] These reactors produce less than 1% of the radioactivity of most land-based nuclear power plants, can move, and are more ruggedly designed than land-based nuclear power plants.

The director of the Office of Science and Technology Policy (OSTP), John H. Marburger III, enacted a directive related to the Public Health Security and Bioterrorism Preparedness and Response Act in 2008 to allow states to obtain waivers to the 20-mile rule.[27] The federal government still supports KI distribution within 10 miles of a nuclear power plant, once again making the federal regulation consistent with the FEMA guidance upon which the DOD policy is based. Instead of providing KI to individuals 10–20 miles away from the power plant, the OSTP director stated that those individuals should be evacuated quickly and instructed to avoid potentially contaminated food or beverages. OSTP performed modeling and surveyed the states along with this change. The modeling suggested that, given the makeup of current U.S. nuclear power plants, the 20-mile radius would likely not be needed. Although states were generally in favor of the decreased requirement,[28] the American Thyroid Association (ATA), was opposed to the new rule.[29]

KI was no longer required to be in the SNS in 2008, per the Public Health Emergency and Medical Countermeasures Enterprise (PHEMCE).[30] The KI that was in the SNS was redistributed to eligible states. The stockpile is maintained at the state level to ensure that it can be distributed in a timely manner. In 2014, the PHEMCE stockpiled KI again in modified quantities in response to what had happened after the 2011 Fukushima-Daiichi accident.

2. World Policy

Since the DOD policy was updated in 2004, the EU and the WHO have updated their policies. Most of the changes to those policies have been minor. Most European countries stockpile KI, as the United States does, for those within 5–50 km of nuclear power plants

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[25] Ibid.

[26] Ibid., 42.

[27] Executive Office of the President, "Decision on Delegation of Section 127(f) of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002" (decision memorandum, Washington, DC: Office of Science and Technology Policy, January 22, 2008), https://www.hsdl.org/?abstract&did=234449.

[28] Ibid.

[29] Angela M. Leung et al., "American Thyroid Association Scientific Statement on the Use of Potassium Iodine Ingestion in a Nuclear Emergency," *Thyroid* 27, no. 7 (July 1, 2017): 865–877, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5561443/pdf/thy.2017.0054.pdf.

[30] National Research Council, *The Science of Responding to a Nuclear Reactor Accident: Summary of a Symposium* (Washington, DC: National Academies Press, 2014), 15, https://doi.org/10.17226/19002.

(most within 20 km).[31] Most European countries stockpile 65-mg KI tablets, although a few, such as the Netherlands and Finland, stockpile 130-mg KI tablets just as the majority of the United States does.[32] The 65-mg tablets, however, make it easier to give children (the most vulnerable group to radioactive iodine) the correct dose of KI.

The WHO guidance was updated in 2017.[33] The updates were minor, and U.S. guidelines are still in line with the WHO guidance. Most updates provided greater scientific backing behind the low rate of side effects and need for KI early after exposure.[34] The more recent scientific literature referenced by the WHO guidance is discussed in Subsection 2.D.2.

D. Updates in Scientific Literature

1. Historical Research

Most of the information on KI and the risk of ^{131}I to children comes from Chernobyl. U.S. nuclear power plants are constructed differently and have better safety features than the power plant at Chernobyl, so the range of effect would likely be smaller if a U.S. nuclear accident were to occur in the future.[35] However, the benefit of having KI, given a risk of radioiodine, can be extrapolated from those around Chernobyl. Between 1991 and 2015, nearly 20,000 individuals who were children at the time of the Chernobyl accident and living in Belarus, Ukraine, or the four contaminated regions of Russia were diagnosed with thyroid cancer.[36] Few individuals were given KI outside of Poland. Scientists estimated that the fraction of the incidence of thyroid cancer that was attributable to Chernobyl-related radiation was 0.25, with an uncertainty of 0.07–0.5. The data were insufficient to determine whether an increase in thyroid cancer risk occurred for those *in utero* at the time of the accident.[37] Aside from those *in utero* at the time of the accident, the risk of thyroid cancer following Chernobyl decreased with increasing age up to adulthood. Those who lived in regions with high iodine sufficiency had lower rates of thyroid cancer than those

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[31] J. R. Jourdian and K. Herviou, *Radiation Protection NO 165: Medical Effectiveness of Iodine Prophylaxis in a Nuclear Reactor Emergency Situation and Overview of European Practices* (Brussels, Belgium: European Union, 2010), 42–43, https://ec.europa.eu/energy/sites/ener/files/documents/165.pdf.

[32] Ibid., 29.

[33] World Health Organization (WHO), *Iodine Thyroid Blocking: Guidelines for Use in Planning for and Responding to Radiological and Nuclear Emergencies* (Geneva, Switzerland: World Health Organization, 2017), https://www.who.int/ionizing_radiation/pub_meet/iodine-thyroid-blocking/en/.

[34] Ibid., 6–8.

[35] National Research Council, *Distribution and Administration of Potassium Iodide*, 5.

[36] United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), "Evaluation of Data on Thyroid Cancer," v.

[37] Elaine Ron, "Thyroid Cancer Incidence Among People Living in Areas Contaminated by Radiation from the Chernobyl Accident," *Health Physics* 93, no. 5 (November 2007): 506, doi:10.1097/01.HP.0000279018.93081.29.

who lived in regions with low iodine sufficiency.[38] Some of these trends were also seen in survivors of the atomic bombs; however, those studies were performed decades after the exposure, and no one had been given KI in the aftermath.[39]

In Poland, the government encouraged people to stop consuming contaminated milk and local vegetables and gave out doses of KI three to six days after the accident. Even though KI was given days after the accident, it was protective because people were still eating and drinking contaminated foods and milk at that time. Few children had adverse side effects from the KI administration. The distribution of thyroid hormone levels a few years after the accident was consistent with those who were not given KI. However, in people who were newborns at the time, 0.37% (12 of 3,214) of those who received KI had a transient increase in thyroid hormones. Only 4.6% of 12,040 total children and 4.5% of 5,061 total adults reported non-thyroid side effects after KI ingestion, most of which were vomiting and skin rashes. Only 19% of those who reported adverse side effects sought a physician, and 80% of those required no further medical attention (0.2% had medically significant side effects). Some of the side effects noted could also have been due to panic following the nuclear power plant accident rather than the KI itself. Two adults (and no children) had severe reactions to KI, but both adults had prior iodine sensitivity. Thus, KI was well-received, with generally minimal and temporary side effects.[40]

2. Updated Research

The only major nuclear power plant accident that has occurred since 2004 was the Fukushima Daiichi accident in 2011. The Fukushima Daiichi disaster did not produce any increase in thyroid cancer within the first 4 years after the accident among children nearby, unlike the aftereffects of Chernobyl[41]—likely because the meltdown released only 10% of the petabecquerels of ^{131}I that the meltdown at Chernobyl released and people in Japan had a much higher dietary iodine intake than those in Belarus or Ukraine.[42] Most individuals did not receive KI following the Fukushima Daiichi nuclear power plant accident.[43]

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[38] Ibid., 506–507.

[39] Preston et al., "Solid Cancer Incidence," 43.

[40] The information in this paragraph comes from Janusz Naumann and Jan Wolff, "Iodide Prophylaxis in Poland after the Chernobyl Reactor Accident: Benefits and Risks," *The American Journal of Medicine* 94, no. 5 (May 1993): 524–532, https://doi.org/10.1016/0002-9343(93)90089-8.

[41] Shinichi Suzuki et al., "Comprehensive Survey Results of Childhood Thyroid Ultrasound Examinations in Fukushima in the First Four Years After the Fukushima Daiichi Nuclear Power Plant Accident," *Thyroid* 26, no. 6 (2016): 843, doi:10.1089/thy.2015.0564.

[42] Ibid.

[43] Hajime Watanobe et al., "The Thyroid Status of Children and Adolescents in Fukushima Prefecture Examined during 20–30 Months after the Fukushima Nuclear Power Plant Disaster: A Cross-Sectional, Observational Study," *PLoS One* 9, no. 12 (December 4, 2014): e113804 (8 of 19), https://doi.org/10.1371/journal.pone.0113804.

Some research has been done to determine the success of different predistribution methods. The Michigan Department of Community Health mailed vouchers to people within 10 miles of a nuclear power plant so they could pick up KI for their homes.[44] Only 5.3% of people redeemed their vouchers, and half of those did not know what KI was used for. The government therefore decided that better public messaging was required, although the Department of Community Health had informed media outlets, hosted public forums, and posted on their website about the program before mailing the vouchers.[45] In the Kagoshima Prefecture of Japan, the government successfully predistributed KI to half of residents within a 5-km radius of nuclear facilities (2,420 of 4,715 individuals).[46] The Prefecture held a series of meetings on KI and distributed the tablets at the meetings. This predistribution method was limited because they could not distribute the proper dose to those under 3 years old—even though babies and toddlers would be the most likely group affected by radioactive iodine—since they did not have small enough tablets or liquid preparations.[47]

Although the low frequency of adverse effects following KI administration was known when the DOD policy was issued, it has been further confirmed with subsequent research. Adverse effects of KI are infrequent and largely tied to preexisting conditions found almost exclusively in older individuals, newborns, infants, or those given large doses of KI over long periods of time (much greater than the dose prescribed following a nuclear power plant accident).[48] Hypothyroidism or other thyroid disorders, found most often in adults, can be associated with increased adverse thyroid effects following KI use. Newborns or infants are more likely to receive excessive doses since the tablets are difficult to break into the appropriate size and newborns or infants may have more adverse effects, although little research has been conducted on this issue.[49] Even in the at-risk groups, most of the adverse effects following KI treatment were minor (e.g., transient changes in thyroid hormone levels or dermatitis).

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[44] Laura R. Zwolinski, Martha Stanbury, and Susan Manente, "Nuclear Power Plant Emergency Preparedness: Results from an Evaluation of Michigan's Potassium Iodide Distribution Program," *Disaster Medicine and Public Health Preparedness* 6, no. 3 (October 2012): 263, https://doi.org/10.1001/dmp.2012.41.

[45] Ibid.

[46] Mayo Ojino et al., "First Successful Pre-Distribution of Stable Iodine Tablets Under Japan's New Policy After the Fukushima Daiichi Nuclear Accident," *Disaster Medicine and Public Health Preparedness* 11, no. 3 (June 2017): 365–369, https://doi.org/10.1017/dmp.2016.125.

[47] Ibid., 367.

[48] L. Spallek et al., "Adverse Effects of Iodine Thyroid Blocking: A Systematic Review," *Radiation Protection Dosimetry* 150, no. 3 (2012): 267–277, doi:10.1093/rpd/ncr400.

[49] Ibid., 274.

One study found that the efficacy of KI may drop off more suddenly over time relative to time of exposure than was previously thought.[50] When 100 mg of KI was given to 27 participants (aged 22 to 46, with a median age of 25 years) 24 hours before exposure to ^{123}I, the dose of ^{123}I was reduced by 88.7%. When given 2 or 8 hours after exposure, the dose was reduced by 63.8% or 21.5%, respectively. This reduction was smaller than had been assumed in the FDA guidance. The younger participants (22–25 years old, n = 20) had smaller reductions than older participants, but the cohorts were small. No studies have been performed to analyze whether children would have smaller reductions in radioactive iodine dose. Most other studies on the efficacy of KI administration were either performed decades ago or only using computer modeling rather than real-world data.[51] Händscheid et al.'s study may suggest then that it would be even more important than previously thought to give individuals KI as soon as possible after exposure to radioactive iodine. More information would be required, however, to determine whether giving individuals KI as soon as possible after exposure would affect the radius around a nuclear power plant for which KI should be stockpiled.

E. Recommendations

Little additional scientific research has been done since the DOD policy was issued in 2004, and almost none of it is counter to current guidance. The stockpiling regulations have since changed but have reverted back to the state referenced in the DOD policy. Since the guidance for KI predistribution is now primarily done at the state level, we recommend that DOD ensure that it has access to enough KI at its bases in each state so that military personnel and their families can receive the proper dosage in time. Having enough access to KI at its bases in each state may require additional stockpiling at the military base if the current state's stockpiling system does not allow children on DOD bases to receive KI promptly after a nuclear power plant accident. The number of doses the military base can keep on site should be coordinated with the state. DOD also should stockpile smaller tablets or liquid doses so that newborns and young children, the population most affected by radioactive iodine, can receive the proper dose.

The following suggested recommendations may help update or strengthen policy regarding KI:

- Assess DOD stockpile of KI and potentially adjust stockpile to improve preparedness to provide KI to children.

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[50] Heribert Hänscheid et al., "Facing the Nuclear Threat: Thyroid Blocking Revisited," *Journal of Clinical Endocrinology and Metabolism* 96, no. 11 (November 2011): 3511–3516, https://doi.org/10.1210/jc.2011-1539.

[51] M. Jang et al., "Age-Dependent Potassium Iodide Effect on the Thyroid Irradation by ^{131}I and ^{133}I in the Nuclear Emergency," *Radiation Protection Dosimetry* 130, no. 4 (July 2008): 499–502, https://doi.org/10.1093/rpd/ncn068.

  - For select areas and stockpiles, include 32-mg tablets or liquid doses of KI, which are necessary and more appropriate dosages for children, in addition to the currently stockpiled 130-mg tablets.

- Ensure that stockpiles of KI are positioned within 10 miles of a nuclear power plant (either in the United States or outside the United States) so that those most likely to be affected can receive doses within four hours. Complying with this recommendation may require additional stockpiling at military bases, along with state stockpiles.

3. Prussian Blue

A. Introduction

RDDs are devices that distribute radioactive material that contaminates the surrounding area and are one of the most common threats associated with radioactive cesium.[52] RDDs can be a radioactive source that emits radiation (a radiation emitting device (RED)) or an explosive device that disperses radioactive material (i.e., a "dirty bomb") and can be made with radioactive sources stolen from industrial sites or hospitals or "orphan" sources that have been lost, abandoned, or are otherwise unaccounted for.[53] RDDs can cause external and internal exposure: contaminated dust or objects could cause external exposure, while inhaling aerosolized radioactive material would cause internal exposure.[54] Radioactive ^{137}Cs is one of the most likely radiological sources to be used in RDDs.[55] Radioactive cesium emits beta and gamma radiation, which makes it an internal and external hazard.[56]

Radioactive cesium sources are the second most commonly stolen radioactive sources, with 53 recorded incidents between 1993 and 1998.[57] According to the National Council on Radiation Protection and Measurements (NCRP), the most common cesium sources are industrial plants, laboratories, hospitals, and aged fission products.[58] These sources can output a range of radioactivity, some examples of which are listed in Table 2.

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[52] Alexis Rump et al., "Medical Management of Victims Contaminated with Radionuclides after a 'Dirty Bomb' Attack," *Military Medical Research* 5, no. 27 (2018): 2, doi:10.1186/s40779-018-0174-5.

[53] Charles D. Ferguson, Tahseen Kazi, and Judith Perera, *Commercial Radioactive Sources: Surveying the Security Risks*, Occasional Paper # 11 (Monterey, CA: Center for Nonproliferation Studies, Monterey Institute of International Studies, January 2003), v, vii, http://hps.org/documents/MontereyReport.pdf.

[54] Ibid., 18–19.

[55] Carl A. Curling and Alex Lodge, *Review of Radioisotopes as Radiological Weapons*, IDA Document D-8048 (Alexandria, VA: Institute for Defense Analyses, June 2016), 45.

[56] "Radioisotope Brief: Cesium-137 (Cs-137)," Centers for Disease Control and Prevention (CDC), last updated April 4, 2018, accessed October 28, 2019, https://www.cdc.gov/nceh/radiation/emergencies/isotopes/cesium.htm.

[57] Ferguson, Kazi, and Perera, *Commercial Radioactive*, 14.

[58] W. J. Bair et al., *Management of Persons Contaminated with Radionuclides*, NCRP Report No. 161-I (Bethesda, MD: National Council on Radiation Protection and Measurements, 2008), 204.

Table 2. Comparative Examples of Source Radioactivity

Product	Radioactivity	Notes
Goiânia source	1,375 Ci[a]	
Gray Star food irradiators	2.8 million Ci[a]	Cesium chloride powder[a]
Industrial sources	2.16×10^5 Ci[b]	8×10^{15} Bq – usually 1 cm x 50 cm[b]
DOE blood irradiators (PNNL)	13,500 Ci[a]	Specific activity of 88 Ci/g[a]

[a] Charles D. Ferguson, Tahseen Kazi, and Judith Perera, *Commercial Radioactive Sources: Surveying the Security Risks*, Occasional Paper # 11 (Monterey, CA: Center for Nonproliferation Studies, Monterey Institute of International Studies, January 2003), http://hps.org/documents/MontereyReport.pdf.

[b] International Atomic Energy Agency (IAEA), *Disposal Options for Disused Radioactive Sources*, Technical Reports Series No. 436 (Vienna, Austria: IAEA, 2005), https://www-pub.iaea.org/MTCD/publications/PDF/TRS436_web.pdf.

Note: The abbreviations in this table are defined in Appendix C of this paper.

Curies are a measure of the activity of a radioactive source that is dependent on the half-life and mass of a given source. As a comparison, brain scans use only millicuries, while nuclear medicine generators typically produce on the scale of Curies.[59]

Prussian blue is the common name for ferric hexacyanoferrate (II), which is used to treat internal cesium exposure. Prussian blue is insoluble in water and binds cesium by ion exchange within the gastrointestinal (GI) tract to reduce its time in the body.[60] By changing the primary elimination route from urinary to fecal, Prussian blue reduces the uptake of cesium into the bloodstream.[61] It is FDA-approved for use in treating cesium and thallium exposure and is most effective when given within 24 hours of exposure.[62]

B. Current DOD Policy

The current DOD guidance, DOD Policy 05-007, follows FDA guidelines for Prussian blue.[63] FDA guidelines for the use of Prussian blue in the treatment of internal cesium and thallium contamination were approved in 2003. These guidelines were based on the

[59] Washington State Department of Health, "How Do We Compare Activity and Dose?," Fact Sheet 320-059 (Turnwater, WA: Division of Environmental Health, Office of Radiation Protection, January 2003), 4, https://www.doh.wa.gov/Portals/1/Documents/Pubs/320-059_compdose_fs.pdf.

[60] D. G. Jarrett et al., "Use of Prussian Blue (Radiogardase™) for Treatment of Internal Radiocesium Contamination" (Bethesda, MD: Armed Forces Radiobiology Research Institute, August 2005), 1, https://www.usuhs.edu/sites/default/files/media/afrri/pdf/use-of-prussian-blue.pdf.

[61] John F. Kalinich, "Treatment of Internal Radionuclide Contamination," in *Medical Consequences of Radiological and Nuclear Weapons,* ed. Martha K. Lenhart (Falls Church, VA: Office of the Surgeon General, 2012), 77, https://web.archive.org/web/20161201222323/http:/www.cs.amedd.army.mil/borden/Portlet.aspx?id=b3cb37ed-08e7-4617-a40c-f148ee3d2303.

[62] Department of Defense, "Policy for the Use of Prussian Blue for Protection of United States Personnel," Policy 05-007 (memorandum, Washington, DC: Office of the Assistant Secretary of Defense for Health Affairs (OASD(HA)), July 13, 2005), 1, https://health.mil/Reference-Center/Policies/2005/07/13/Policy-for-the-Use-of-Prussian-Blue-for-Protection-of-United-States-Personnel.

[63] Ibid.

need for MCMs after terrorist attacks or dirty bombs[64] and were updated in 2014.[65] The product label for Radiogardase, the FDA-approved formulation of Prussian blue, recommends beginning treatment as soon as possible after contamination is suspected but also recommends gathering a quantitative baseline before beginning treatment, if possible.[66] This discrepancy—treatment as soon as possible after contamination vs. treatment after gathering a quantitative baseline—highlights the lack of consensus on the appropriate time to start Prussian blue treatment. As with most medications, obtaining as much relevant information as possible is helpful in making an informed prescriptive decision because a baseline exposure can inform the treatment length. However, the sooner Radiogardase is taken, the sooner it starts working, and radiation treatment should generally not be delayed.

Radiogardase is a 500-mg capsule that should be taken with food. It is given three times daily in 3-g doses for adults (total daily dose of 9 g) and 1-g doses for children (total daily dose of 3 g). It is not FDA-approved for infants under 2 years of age[67] due to lack of data in the age group and difficulty solubilizing it into a liquid formula.[68] Some recommendations suggest that Prussian blue should only be used in cases in which the radiation dose is 1–10 times higher than the annual limit on intake (ALI);[69] however, this topic is still controversial and consensus has not yet been reached. Regardless, the FDA recommends treating with Prussian blue for at least 30 days or until whole body dose is less than one ALI.[70] It is also recommended that Prussian blue be stocked at the regional or national level. While local response is critical and Prussian blue is immediately effective, it is still effective after a delay that would allow for more urgent life-saving efforts.[71]

Radiogardase has no contraindications and has limited side effects (e.g. possible constipation and asymptomatic hypokalemia, or low potassium levels in the blood). Clinical studies—mostly based on the 1987 Goiânia incident—showed that Radiogardase reduced the whole-body effective half-life of ^{137}Cs by 69% in adults, 46% in adolescents, and

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[64] "FDA Approves First New Drug Application for Treatment of Radiation Contamination Due to Cesium or Thallium," U.S. Food and Drug Administration (FDA), October 2, 2003, last updated March 8, 2018, accessed May 29, 2019, https://www.fda.gov/drugs/bioterrorism-and-drug-preparedness/fda-approves-first-new-drug-application-treatment-radiation-contamination-due-cesium-or-thallium.

[65] U.S. Department of Health and Human Services, "Highlights of Prescribing Information: RADIOGARDASE (Prussian Blue Insoluble) Capsules" (Rockville, MD: Food and Drug Administration, August 2014), https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021626s010lbl.pdf.

[66] Ibid., 2

[67] Ibid., 2, 5.

[68] Aaron H. Gardner et al., "Medical Countermeasures for Children in Radiation and Nuclear Disasters: Current Capabilities and Key Gaps," *Disaster Medicine and Public Health Preparedness* 13, no. 3 (June 2019): 644, https://doi.org/10.1017/dmp.2018.112.

[69] Kristi L. Koenig et al., "Medical Treatment of Radiological Casualties: Current Concepts," *Annals of Emergency Medicine* 45, no. 6 (June 2005): 649, https://doi.org/10.1016/j.annemergmed.2005.01.020.

[70] Ibid.

[71] Ibid., 650.

43% in young children.[72] Treatment typically lasts a minimum of 30 days. Radiogardase is included in the SNS and an Emergency Use Authorization (EUA) may be activated to provide infants under age 2 with Radiogardase in a mass casualty emergency.[73] The SNS reportedly has "thousands of treatment courses" of Prussian blue.[74] Because Prussian blue is still effective after a short delay, the time it takes to distribute it from the SNS would likely not significantly affect its efficacy. Health and Human Services (HHS) performs an annual inventory of the SNS, including routine quality assurance and ensuring that individual materials are rotated out to stay within their expiration date. However, the DOD and FDA can use the Shelf Life Extension Program to grant additional time (typically 12–24 months) to expiration dates if testing determines the drug is stable and adequate for continued use.[75] Although doctrine recommends following FDA guidelines, the Army dosing guidelines differ from FDA guidance by stating 1 g, rather than 3 g, orally, mixed in 100–200 mL water three times a day for adults. The doctrine does follow FDA guidelines in that it should be taken as soon as possible but can still be effective if given after a delay of a few days.[76]

It is recommended that field medical treatment facilities (MTFs) be located 30–50 meters upwind of a decontamination site. When receiving patients potentially contaminated with ^{137}Cs, a chest-level reading of 0.1 mR/hour indicates likely internal contamination, which should be treated at field MTFs, if possible.[77] The Armed Forces Radiobiology Research Institute (AFRRI) recommends that personnel who are externally contaminated and did not have respiratory protection be examined for potential internal contamination.

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[72] U.S. Department of Health and Human Services, "Highlights of Prescribing Information: RADIOGARDASE," 9.

[73] "Prussian Blue, Insoluble (Radiogardase®)," U.S. Department of Health and Human Services, Radiation Emergency Medical Management (REMM), accessed August 21, 2019, https://www.remm.nlm.gov/prussianblue.htm.

[74] Department of Health and Human Services, "Office of the Assistant Secretary for Preparedness and Response; HHS Public Health Emergency Medical Countermeasures Enterprise Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats," *Federal Register* 72, no. 77 (April 23, 2007): 20118, https://www.govinfo.gov/content/pkg/FR-2007-04-23/pdf/07-1983.pdf.

[75] "Sustaining the Stockpile," U.S. Department of Health and Human Services, accessed October 8, 2019, https://www.phe.gov/about/sns/Pages/sustaining.aspx.

[76] Headquarters, Department of the Army, *Multiservice Tactics, Techniques, and Procedures for Treatment of Nuclear and Radiological Casualties,* ATP 4-02.83/MCRP 4-11.1B/NTRP 4-02.21/AFMAN 44-161(I) (Washington, DC: HQDA, May 2014), A-4, https://armypubs.army.mil/epubs/DR_pubs/DR_a/pdf/web/atp4_02x83.pdf.

[77] John P. Madrid, "Radiological Considerations in Medical Operations," in *Medical Consequences of Radiological and Nuclear Weapons,* ed. Martha K. Lenhart (Falls Church, VA: Office of the Surgeon General, 2012), 235–236, https://web.archive.org/web/20161201222323/http:/www.cs.amedd.army.mil/borden/Portlet.aspx?id=b3cb37ed-08e7-4617-a40c-f148ee3d2303.

For cesium, rubidium, and thallium internal exposure, AFRRI follows FDA dosing instructions for Prussian blue (3 g given three times per day for adults, and 1 g given three times per day for children),[78] unlike the current Army guidelines as previously mentioned.[79]

In a mass casualty situation following a nuclear or radiological incident, local medical supplies are likely to run low within 24–48 hours.[80] The *Planning Guide for Response to a Nuclear Detonation* states that significant federal response is likely to arrive to a nuclear event site 24–72 hours later, emphasizing the importance of local emergency response. Furthermore, the *Planning Guide* suggests that Prussian blue is not useful in the early medical response phase;[81] rather, immediate life-saving measures are the most time sensitive, given that Prussian blue is still effective when given after a delay.

Homeland Security Presidential Directive 18 (HSPD-18) states that MCM stockpiling should focus on catastrophic events (e.g., improvised nuclear devices (INDs) and RDDs) and agents whose effects are able to be mitigated with medical care; furthermore, it should be rapidly deployable yet flexible.[82] The North Atlantic Treaty Organization (NATO) states that individual nations are responsible for stockpiling enough MCMs for their deployed troops and for ensuring that resupply chains are uninterrupted.[83] HSPD-21 states a desire to pivot from surging existing healthcare capabilities to preparing the healthcare system in advance to be ready to coordinate and rapidly deploy materiel and personnel. It also states that MCMs would ideally be distributed to an affected population within 48 hours and that HHS (and other agencies, such as DOD and the Department of Homeland Security (DHS)) should share MCMs between the SNS and other stockpiles, including

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[78] Ronald E. Goans, *Medical Management of Radiological Casualties*, 4th ed. (Bethesda, MD: Armed Forces Radiobiology Research Institute, July 2013), 28, 30–31, 33, https://pdfs.semanticscholar.org/ad46/c537cf2671f5e5b77ba08ea3e4a6ad4dc4fb.pdf?_ga=2.6031159.580949267.1581694575-1362152443.1575645517.

[79] Headquarters, Department of the Army, *Multiservice Tactics, Techniques, and Procedures for Treatment of Nuclear and Radiological Casualties*, A-4.

[80] Daniel F. Flynn and Ronald E. Goans, "Triage and Treatment of Radiation and Combined-Injury Mass Casualties," in *Medical Consequences of Radiological and Nuclear Weapons*, ed. Martha K. Lenhart (Falls Church, VA: Office of the Surgeon General, 2012), 59, https://web.archive.org/web/20161201222323/http:/www.cs.amedd.army.mil/borden/Portlet.aspx?id=b3cb37ed-08e7-4617-a40c-f148ee3d2303.

[81] National Security Staff Interagency Policy Coordination Subcommittee for Preparedness and Response to Radiological and Nuclear Threats, *Planning Guidance for Response to a Nuclear Detonation*, 2nd ed. (Washington, DC: Executive Office of the President, June 2010), 92, https://www.remm.nlm.gov/PlanningGuidanceNuclearDetonation.pdf.

[82] The White House, "Directive on Medical Countermeasures Against Weapons of Mass Destruction," Homeland Security Presidential Directive/HSPD-18 (January 31, 2007), *Weekly Compilation of Presidential Documents* 43, no. 6 (February 12, 2007): 129, https://www.hsdl.org/?abstract&did=456436.

[83] North Atlantic Treaty Organization (NATO), *Commander's Guide on Medical Support to Chemical, Biological, Radiological, and Nuclear (CBRN) Defensive Operations*, Edition A Version 1, STANAG 2873 (Brussels: NATO, February 2018), 6-2–6-3.

forging reciprocal agreements with international stockpiles.[84]Army doctrine states that the placement of specific MCMs is determined by the combatant commanders based on deployment locations and situations.[85] The United States has Prussian blue stockpiled at four global locations: U.S. Army Medical Materiel Center Europe (Germany), Tripler Army Medical Center (Hawaii), Walter Reed Army Medical Center (Maryland), and Brooke Army Medical Center (Texas). It can be distributed from these locations to the medical treatment unit within 24 hours.[86]

Prussian blue has been included in the WHO's List of Essential Medicines since at least the 12th iteration in 2002[87] and was once again included in the 19th version in 2019.[88] Furthermore, the WHO outlines certain guidelines when considering how to stockpile MCMs. It emphasizes that local health care capabilities are the backbone of radiological incident response, while federal and international capabilities should be available for support. It is assumed that a WHO stockpile response will arrive around 48 hours post-incident, so stockpiling enough MCMs to treat 200 people for 10 days is recommended. This suggestion is derived from the assumption that in a mass casualty incident, 2,000–20,000 people may present for treatment (including worried well), but that only 1%–10% of those people would actually require treatment. Given the WHO-recommended dosing schedule of 3 g/day for adults (unlike the total 9 g/day recommended in the FDA dosing guidance), a total of 12,000 Prussian blue capsules would be required to treat 200 people for 10 days.[89] If FDA guidance were followed or if more people require treatment, then the required stockpile would be much larger.

The NCRP also follows FDA guidance in its own publications. It recommends the same doses for adults and adolescents and the same treatment duration and also recommends exercising caution in prescribing Prussian blue to patients with pre-existing cardiac

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[84] The White House, "Public Health and Medical Preparedness," Homeland Security Presidential Directive/HSPD-21 (Washington, DC: Office of the Press Secretary, October 18, 2007), 4, 7, https://www.hsdl.org/?abstract&did=480002.

[85] Headquarters, Department of the Army, *Multi-Service Tactics, Techniques, and Procedures for Health Service Support in a Chemical, Biological, Radiological, and Nuclear Environment*, ATP 4-02.7/MCRP 4-11.1F/NTTP 4-02.7/AFTTP 3-42.3 (Washington, DC: HQDA, March 2016), 2-7, https://armypubs.army.mil/epubs/DR_pubs/DR_a/pdf/web/atp4_02x7.pdf.

[86] Department of Defense, "Policy for the Use of Prussian Blue," 2.

[87] World Health Organization, "Essential Medicines: WHO Model List," 12th ed. (Geneva, Switzerland: World Health Organization, April 2002), 4, https://apps.who.int/iris/bitstream/handle/10665/67335/a76618.pdf?sequence=1.

[88] World Health Organization, "Model List of Essential Medicines," 21st List (Geneva, Switzerland: World Health Organization, 2019), 4, https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1.

[89] M. Perez and Z. Carr, eds., "Development of Stockpiles for Radiation Emergencies: Report of the Radio-Nuclear Working Group" (Geneva, Switzerland: WHO Headquarters, 14–16 February 2007), 31, https://www.who.int/ionizing_radiation/a_e/emergencies/WHO_stockpile_report_2007.pdf.

arrhythmias or electrolyte imbalances (since Prussian blue has the potential to cause hypokalemia).[90]

C. Changes to U.S. and World Policy Since 2005

Policy regarding DOD's use of Prussian blue has not changed since the current policy was enacted in 2005. Most policies adhere to FDA guidelines or point back to the FDA guidance. The Environmental Protection Agency (EPA) Protective Action Guides underwent revisions and updates between the 1992 and 2017 editions, but guidance relating specifically to Prussian blue did not change. For radiological incidents, the scope was expanded to included scenarios such as nuclear power plant incidents, general radiological incidents (including RDDs and INDs), transportation accidents, and medical manufacturing incidents. Dosimetry and assessment methods in general were updated, while limits of exposure were unchanged.[91]

D. Updates in Scientific Literature

1. Historical Research

Most data on the efficacy and clinical effects of Prussian blue came out of the 1987 Goiânia incident in Brazil. On September 13, 1987, a shielded ^{137}Cs teletherapy source was removed from an abandoned clinic in Goiânia. The source was broken in the process of being passed around by people in the village, who were intrigued by the blue glow emanating from the source. A total of 28 people suffered radiation burns, and 4 people died. In addition, extensive contamination yielded 3,500 m^3 of radioactive waste.[92] In the aftermath, 46 people were treated with Prussian blue—an undertaking that was anticipated to deplete Brazil's entire stock of Prussian blue. Adults received doses of 4–6 g/day (if they received greater than five times the recommended annual intake level of ^{137}Cs) or 3 g/day, while children received 1–1.5 g/day.[93] The threshold of effectiveness appeared to be 3 g/day, which was given in three 1-g doses.[94] Of the 46 treated patients, 10 had constipation, 11 had light to moderate upper abdominal pain that continued for 6 months post-treatment, and 3 had low serum potassium; however, the low potassium levels were due to Acute

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[90] W.J. Bair et al., *Management of Persons Contaminated with Radionuclides*, 203–204.

[91] United States Environmental Protection Agency (EPA), *PAG Manual: Protective Action Guides and Planning Guidance for Radiological Incidents*, EPA-400/R-17/001 (Washington, DC: Office of Radiation and Indoor Air, Radiation Protection Division, January 2017), 2, 4, https://www.epa.gov/sites/production/files/2017-01/documents/epa_pag_manual_final_revisions_01-11-2017_cover_disclaimer_8.pdf.

[92] International Atomic Energy Agency (IAEA), *The Radiological Accident in Goiânia* (Vienna, Austria: IAEA, 1988), 11, https://www-pub.iaea.org/MTCD/publications/PDF/Pub815_web.pdf.

[93] Ibid., 43, 46.

[94] Ibid., 89.

Radiation Syndrome (ARS), and the upper abdominal pain could not be linked definitively to Prussian blue.[95] A 1990 study analyzed the impact of Prussian blue use on cyanide uptake (since Prussian blue is ferric hexacyanoferrate (II)) and found that in addition to Prussian blue being minimally taken up by the GI tract (0.03%–0.22% iron absorbed after 7 days), the amount of free cyanide that was absorbed was found to be 0.01 mg/kg (based on 0.42% excreted after 7 days), which is two orders of magnitude lower than the lethal dose[96] and therefore not a risk or concern.

2. Updated Research

Most of the scientific research done on Prussian blue has not significantly changed the knowledge landscape. Most research confirms the initial research performed after the Goiânia incident or minimally expands on existing knowledge. Prussian blue is most effective at a pH of 7.5 and experiences reduced efficacy in more acidic conditions. Absorption reductions due to acidic gastric conditions (which can reduce the ion binding of Prussian blue) can largely be avoided through formulation strategies such as pH-specific release. It has no known contraindications and is well-tolerated and considered non-toxic. Few side effects exist, mostly mild constipation and asymptomatic hypokalemia.[97]

While Prussian blue is not currently FDA approved for use in infants under 2 years old, a pre-EUA has been submitted for infants 6–23 months old. Prussian blue cannot be solubilized in formula to give to infants under 6 months old.[98] A 2014 Public Meeting of the U.S. National Advisory Committee on Children and Disasters stated that advances have been made in developing Prussian blue delivery systems for children and infants.[99] Furthermore, Heyltex Corporation was awarded a contract in 2011 to research, develop, and obtain FDA approval for a Radiogardase formulation for infants under 2 years old.[100] As of 2019, no public data regarding this research or its outcome were available.[101]

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[95] United States Environmental Protection Agency (EPA), "Provisional Peer-Reviewed Toxicity Values for Prussian Blue (Ferric Ferrocyanide)," EPA/690/R-05/020F (Cincinnati, OH: Superfund Health Risk Technical Support Center, National Center for Environmental Assessment, Office of Research and Development, 2005), 3–4, https://cfpub.epa.gov/ncea/pprtv/documents/PrussianBlueFerricFerrocyanide.pdf.

[96] Ibid., 4.

[97] Marina Altagracia-Martinez et al., "Prussian Blue as an Antidote for Radioactive Thallium and Cesium Poisoning," *Orphan Drugs: Research and Reviews* 2 (2012): 16, https://doi.org/10.2147/ODRR.S31881.

[98] Gardner et al., "Medical Countermeasures for Children," 644.

[99] Pierre-André Dubé and Sophie Gosselin, "Prussian Blue," in *Critical Care Toxicology*, ed. J. Brent, K. Burkhart, P. Dargan, B. Hatten, B. Megarbane, and R. Palmer (New York, NY: Springer International Publishing, 2016), 4, https://link.springer.com/referenceworkentry/10.1007%2F978-3-319-20790-2_167-1.

[100] Altagracia-Martinez et al., "Prussian Blue as an Antidote," 19.

[101] Gardner et al., "Medical Countermeasures for Children," 644.

Despite all the research performed during and after the Goiânia incident and in laboratories, a general lack of consensus remains on the correct timing of beginning treatment. Two main areas of thought are the "urgent" approach and the "precautionary" approach. The urgent approach begins treatment as soon as possible if exposure is suspected and discontinues treatment when dosimetry confirms lack of exposure or sufficient reduction in whole-body dose. This approach maintains that earlier treatment is more effective. For Prussian blue, delaying treatment by as much as 28 days has been shown to still be effective,[102] although less so than immediate treatment. However, a longer treatment duration may provide some limited advantage to make up for the later start time. The precautionary approach does not begin treatment until confirmation of a committed effective dose equivalent (CEDE) that warrants treatment (> 20–200 mSv). This approach delays treatment so as to not risk potential adverse side effects unless proven necessary. Although Prussian blue has the potential to cause hypokalemia, only a few Goiânia patients were affected, and they exhibited subclinical disturbances. Although no overarching consensus has been reached, the "urgent" approach has been deemed by many to be appropriate for Prussian blue even though it depends on incident scale and stockpile supplies.[103]

It is currently unlikely that most hospitals carry Prussian blue, especially in sufficient quantities to be prepared for a mass casualty incident.[104] In 2018, however, an expert panel that determines guidelines for stocking medicines in hospitals reached a consensus and recommended that Prussian blue be stocked more broadly in emergency care centers and hospitals[105] In the related 2009 panel, the experts could not reach a consensus,[106] and Prussian blue was not even included for consideration in the 2000 meeting.[107] The 2018 panel concluded that priority stockpiling should be placed with hospitals in rich industrial areas (i.e., where radiological accidents may occur). It also calculated how much should be stocked based on treating a patient that weighed 100 kg. Treating one patient for 8 hours would require 12.5 g, and treating one patient for 24 hours would require 25 g.[108]

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[102] Alexandra Leiterer et al., "Medical Countermeasures after a Radiological Event: An Update from the CATO Project," *International Journal of Radiation Biology* 90, no. 11 (November 2014): 1045, https://doi.org/10.3109/09553002.2014.922715.

[103] Rump et al., "Medical Management of Victims Contaminated with Radionuclides," 6–8.

[104] Dubé and Gosselin, "Prussian Blue," 1.

[105] Richard C. Dart et al., "Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care," *Annals of Emergency Medicine* 71, no. 3 (March 2018): 322, https://doi.org/10.1016/j.annemergmed.2017.05.021.

[106] Richard C. Dart et al., "Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care," *Annals of Emergency Medicine* 54, no. 3 (September 2009): 389, https://doi.org/10.1016/j.annemergmed.2009.01.023.

[107] Richard C. Dart et al., "Combined Evidence-Based Literature Analysis and Consensus Guidelines for Stocking of Emergency Antidotes in the United States," *Annals of Emergency Medicine* 36, no. 2 (August 2000): 126–132, https://doi.org/10.1067/mem.2000.108182.

[108] Dart et al., "Expert Consensus Guidelines," (2018), 321.

Prussian blue crystals in Radiogardase bind water to help bind to cesium, and studies have shown that water loss could potentially reduce efficacy and affect other conditions such as pH, exposure time, and particle size. One study analyzed the water loss and binding efficacy of 10-year old Prussian blue samples stored in ideal laboratory/warehouse conditions.[109] Active pharmaceutical ingredient (API) and drug product (DP) formulations were analyzed. APIs experienced 12.58%–22.19% water loss, and DPs experienced 13.38%–25.08% water loss. The pH tests showed that binding was lowest at a pH of 1 and was most effective at a pH of 7.5. After 10 years in storage, the equilibrium binding of Prussian blue to cesium (measured after 24 hours) dropped 10% for APIs and 9% for DPs. The "maximal binding capacity" for one API solution dropped 26%. While the formulations still met FDA cesium binding specifications after 10 years, it was found that 10 years of storage in ideal conditions still reduces the overall efficacy of Prussian blue.[110]

While the FDA-approved dosing guidelines prescribe 3 g given three times daily for adults, which varies from the observed threshold of effectiveness of 3 g/day in Goiânia, many countries have different dosing recommendations. For example, the United Kingdom recommends 1 g given three times daily, Germany prescribes 3–20 g/day, and France recommends 1 g or 3 g given three times daily. Despite these differences, Prussian blue can still be effective if given within 28 days of exposure, and treatment should continue for at least 3 months to reduce the whole-body dose by 40%–55%. No additional benefit has been observed beyond 6 months.[111]

E. Recommendations

Policy and scientific research have not changed significantly since the original doctrine and policy were released in 2005. Radiogardase is an FDA-approved Prussian blue formulation, and, for the most part, the military primarily follows FDA guidance on dosage and use (although the Army follows a different dosing schedule). Most scientific research since 2005 has confirmed initial findings from the 1980s and 1990s following Goiânia, although some deeper understanding has been gained on the impact of storage conditions on efficacy. The following suggested recommendations may help update or strengthen policy regarding Prussian blue:

[109] Adil Mohammad et al., "A Long-Term Stability Study of Prussian Blue: A Quality Assessment of Water Content and Cesium Binding," *Journal of Pharmaceutical and Biomedical Analysis* 103 (25 January 2015): 85–90, https://doi.org/10.1016/j.jpba.2014.10.030.

[110] Ibid., 85, 88–89.

[111] Leiterer et al., "Medical Countermeasures after a Radiological Event," 1045.

- Adjust DOD policy regarding dosing regimen to ensure it is consistent with current Army policy of 1 g three times daily for adults and then provide a definitive administration timeline.
- Review and adjust the Prussian Blue stockpile to ensure that stocked amounts and storage conditions are appropriate.

While DOD's policy is to follow FDA guidance regarding Prussian blue,[112] Army ATP 4-02.83 recommends a different dosing regimen than the FDA.[113] The Army recommends giving 1 g three times daily, while the FDA recommends giving 3 g three times daily. Scientific research indicates that 1 g three times daily is sufficient to treat cesium poisoning in children and adults.[114] In addition, the FDA approval medical review for Radiogardase states that "the optimal dose and dosing schedule has not been determined"[115] and that doses over 3 g/day did not have an additional effect on reducing the whole-body half-life of ^{137}Cs in humans.[116] While DOD recommends making "preferential use" of existing, commercially available FDA-approved MCMs,[117] the DOD and FDA have a memorandum of understanding (MOU) that expands the FDA's ability to issue EUAs for DOD use in CBRN environments, including off-label use of approved products (e.g., a different dosing regimen).[118] The whole DOD should have consistent guidance on dosing, and, given that no concrete scientific evidence exists that 9 g/day is more effective than 3 g/day in humans, DOD should work with the FDA to adopt the lower 3 g/day dosing regimen through a long-standing EUA or other means. This action would also positively impact the stockpiling of Prussian blue. Current stockpiles would be able to protect three times more people with no additional changes.

While no general consensus exists on the administration timeline for Prussian blue in the scientific and public health communities, DOD should decide upon its own concrete administration timeline. Current doctrine is to administer as soon as possible *or* after collecting a quantitative radiation exposure baseline. This doctrine should be clarified to one

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[112] Department of Defense, "Policy for the Use of Prussian Blue," 1.

[113] Headquarters, Department of the Army, *Multiservice Tactics, Techniques, and Procedures for Treatment of Nuclear and Radiological Casualties*, A-4.

[114] International Atomic Energy Agency (IAEA). *The Radiological Accident in Goiânia*, 89.

[115] Center for Drug Evaluation and Research, *Medical Review*, Application Number: 21-626 (Silver, Spring, MD: CDER, September 16, 2002), 42, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-626_Radiogardase_Medr.pdf.

[116] Ibid., 43.

[117] Department of Defense, "Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs," DoDI 6200.02 (Washington, DC: USD(P&R), February 27, 2008), 2, https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/620002p.pdf.

[118] "Memorandum of Understanding Concerning Coordination with the Food and Drug Administration Regarding Department of Defense Medical Product Development and Assessment," Food and Drug Administration, MOU 225-19-001, accessed February 27, 2020, https://www.fda.gov/about-fda/domestic-mous/mou-225-19-001.

or the other. If "as soon as possible," a caveat could be made that quantitative baselines are useful in determining and guiding exposure but that they are not required to begin treatment. If "after collecting an exposure baseline," examination should begin as soon as exposure is suspected. Clarifying discrepancies in DOD policy will improve the guidelines for Prussian blue use, and general consensus is that a more urgent approach is appropriate and efficient for Prussian blue (given that there are little to no side effects, it is more effective when given earlier, and it will placate the "worried well").

DOD (along with related coordinating agencies) should ensure that Prussian blue is sufficiently stocked in stockpiles and is stored correctly. Situations where Prussian blue may be needed are few and far between but may require large quantities when they do happen. Storing Prussian blue in the best possible conditions will ensure that it remains as efficacious as possible for its lifetime. Ensuring proper and sufficient stockpiling of Prussian blue will keep the DOD prepared for radiological incidents.

4. Conclusions

This paper reviews the DOD policies for KI and Prussian blue use against internal radiation exposure, which were issued in 2004 and 2005, respectively. In the past 15 years, some policies have been updated and some additional scientific research has been published. This review aimed to determine whether the DOD policies also needed to be updated.

Most of the major information regarding the adverse side effects, the distribution, and the use of these two countermeasures (KI and Prussian blue) is from events that occurred and were researched before the policies were put in place (Chernobyl for KI and the Goiânia incident for Prussian blue). Most information published since those events confirmed previously found results, and most policy changes that occurred since the original DOD policies were minor or were reversed later. Key recommendations to DOD for updating policy or ensuring that the countermeasures are properly distributed when needed are as follows:

- KI
  - Assess DOD stockpile of KI and potentially adjust stockpile to improve preparedness to provide KI to children.
    - For select areas and stockpiles, include 32-mg tablets or liquid doses of KI, which are necessary and more appropriate dosages for children, in addition to the currently stockpiled 130-mg tablets.
  - Ensure that stockpiles of KI are positioned within 10 miles of a nuclear power plant (either in the United States or outside the United States) so that those most likely to be affected can receive doses within four hours. Complying with this recommendation may require additional stockpiling at military bases, along with state stockpiles.
- Prussian Blue
  - Adjust DOD policy regarding dosing regimen to ensure it is consistent with current Army policy of 1 g three times daily for adults and then provide a definitive administration timeline.
  - Review and adjust the Prussian Blue stockpile to ensure that stocked amounts and storage conditions are appropriate.

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Appendix A.
Illustrations

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Appendix B.
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Appendix C.
Abbreviations

^{131}I	Iodine-131
^{137}Cs	Cesium-137
AFMAN	Air Force Manual
AFRRI	Armed Forces Radiobiology Research Institute
AFTTP	Air Force Tactical Techniques and Procedures
ALI	annual limit on intake
API	active pharmaceutical ingredient
ARS	Acute Radiation Syndrome
ATA	American Thyroid Association
ATP	Army Techniques Publication
Bq	Becquerel
CDER	Center for Drug Evaluation and Research
CEDE	committed effective dose equivalent
cGy	centrigray
Ci	Curie
Ci/g	Curie per gram
CLBN	commercial land-based nuclear
cm	centimeter
DHS	Department of Homeland Security
DNA	deoxyribonucleic acid
DOD	Department of Defense
DODI	Department of Defense Instruction
DOE	Department of Energy
DP	drug product
EPA	Environmental Protection Agency
EPZ	emergency planning zone
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
g	gram
GI	gastrointestinal
HA	Health Affairs
HHS	Health and Human Services
HSPD	Homeland Security Presidential Directive
IAEA	International Atomic Energy Agency
IDA	Institute for Defense Analyses
IND	improvised nuclear device

kg	kilogram
KI	potassium iodide
MCM	medical countermeasure
MCRP	Marine Corps Reference Publication
mg	milligram
mL	milliliter
mR	milliroentgen
mSv	millisievert
MTF	medical treatment facility
NATO	North Atlantic Treaty Organization
NCRP	National Council on Radiation Protection and Measurements
NTRP	Navy Tactical Reference Publication
NTTP	Navy Tactical Techniques and Procedures
OASD(HA)	Office of the Assistant Secretary of Defense for Health Affairs
OSTP	Office of Science and Technology Policy
OTSG	Office of the Surgeon General
PAG	Protective Action Guide
pH	scale that measures how acidic or alkaline something is
PHEMCE	Public Health Emergency and Medical Countermeasures Enterprise
PNNL	Pacific Northwest National Laboratory
RDD	radiological dispersion device
RED	radiation emitting device
REMM	Radiation Emergency Medical Management
SNS	Strategic National Stockpile
STANAG	Standardization Agreement
U.S.	United States
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
USD(P&R)	Under Secretary of Defense for Personnel and Readiness
WHO	World Health Organization
yrs	years

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14. ABSTRACT

Potassium iodide (KI) and Prussian blue are two medical countermeasures that can be used to decrease the effects of internal radiological exposure. Potassium iodide protects the thyroid against Iodine-131 (I-131). I-131 is a product of nuclear fission, and is most often encountered in nuclear reactor accidents. Prussian blue binds radioactive cesium and thallium. Cesium-137 (Cs-137) is a product of nuclear fission and is associated with nuclear reactors and nuclear weapons, as well as medical sources and radiological dispersion devices (RDDs). The DOD policies for KI and Prussian blue have not been updated since 2005 and 2004, respectively. Therefore, there is a risk that patients treated with Prussian blue or KI will not receive medical care that is in sync with the last decade-plus of scientific research. Other associated policies, such as guidelines for the Strategic National Stockpile or FEMA guidelines, could have changed in the interim as well. This paper reviews scientific literature and policies published since 2004 to determine whether or why any changes to the current DOD policies are warranted, and makes recommendations accordingly.

15. SUBJECT TERMS

radiation, medical countermeasures, potassium iodide, Prussian blue, I-131, iodine, Cs-137, cesium, Strategic National Stockpile, DOD policy

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