June 8, 2015

MEMORANDUM TO: Robert Johnson, Chief
Fuel Manufacturing Branch
Division of Fuel Cycle Safety, Safeguards,
and Environmental Review
Office of Nuclear Material Safety
and Safeguards

FROM: James Hammelman, Sr. Chemical Engineer **/RA/**
Fuel Manufacturing Branch
Division of Fuel Cycle Safety, Safeguards,
and Environmental Review
Office of Nuclear Material Safety
and Safeguards

SUBJECT: DISPOSITION OF COMMENTS ON INTERIM STAFF GUIDANCE ON ACUTE URANIUM EXPOSURE STANDARDS FOR WORKERS

The draft interim staff guidance (ISG) on acute uranium intake was issued for public comment in the *Federal Register* on September 17, 2014. The ISG is based on the staff's independent review of the uranium toxicity information. The staff conservatively identified acute uranium intake quantities that would produce consequences similar to the high and intermediate consequence effects identified in Section 70.61 of Title 10 of the *Code of Federal Regulations* (10 CFR).

Nuclear Energy Institute (NEI) submitted comments on November 12, 2014. The NEI letter supported the ISG, recommended its issuance in final form at the earliest opportunity and offered a few specific comments for clarification, which the staff addressed. A second commenter (anonymous) said the ISG looked like a good idea but had no specific comments on the details of the ISG. The disposition of these comments is discussed in the enclosed table (Enclsoure 1).

During an informal discussion between industry and U.S. Nuclear Regulatory Commission staff at the Atlanta FOC on March 4-5 2015, an industry official suggested that the acceptable acute uranium exposure standards presented in the ISG might be in conflict with the existing regulations. This point was not raised in the NEI comments on the draft ISG. The staff identified two sections of 10 CFR Part 70 regulations that discuss uranium intake limits, but they are not considered to be in conflict with the information in the ISG. The first instance is

CONTACT: James Hammelman, NMSS/FCSE/FMB
(301) 415-7526

10 CFR Paragraph 70.61(b)(3) which identifies a high consequence event as an “intake of 30 mg or greater of uranium in soluble form by any individual located outside the controlled area”. This is not in conflict with the ISG which addresses the acute uranium intake that would result in high or intermediate consequences to a worker.

Enclosures:
1. Comments on ISG and Planned Resolution
2. FCSE Interim Staff Guidance ISG-14, Revision 0 Acute Uranium Exposure Standards for Workers

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OFFICE	NMSS/FCSE/FMB	NMSS/FCSE/FMB	NMSE/FCSS/FMB
NAME	JHammelman	TBrockington	RJohnson
DATE	06/ 1 /2015	06/05/2015	06/ 8 /2015

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COMMENTS ON ISG AND PLANNED RESOLUTION

Commenter	Comment	Planned Resolution
NEI	Discussion section: Based on the 2013 *Toxicological Profile for Uranium* issued by the Agency for Toxic Substances and Disease Registry as referenced by NRC, the Draft ISG should clearly state that there are no documented human deaths from exposure to uranium for any route of exposure.	The subject document states that routine exposures of humans to airborne uranium is not associated with increased mortality and brief exposures to high concentrations of UF6 have caused fatalities in humans, but most likely to the resulting exposure to HF. (p. 43) It also states there are no reports of human deaths from oral exposure of uranium compounds. (p. 109) It also states no deaths have been reported in humans as a result of dermal exposure to uranium. (p. 162) A phase was inserted in the second sentence which says “This ATSDR document notes that no human fatalities have been reported as a result of uranium toxicity.”
NEI	Discussion section, sentence 5: NRC should consider beginning the sentence with “Any damage” rather than “The damage” since an “acute” exposure is often times interpreted as resulting in severe damage, although “acute” is also used to describe a brief exposure that does not result in any damage.	The suggested change was made.
NEI	Page 3, Footnote 1: NRC staff may want to determine whether the paper authored by Leggett et al in 2012 was revised since then and, if so, whether the Draft ISG language is impacted.	The paper by Leggett et. al. has not been revised. No change was made to the ISG
NEI	Technical Review Guidance: The parenthetical reference to “class F” material should be corrected to read “Type F” material consistent with other references in the Draft ISG.	The term “Type F” is used throughout the document
Anonymous	Good Idea	No revision in response to comment

FCSE INTERIM STAFF GUIDANCE ISG-14, REVISION 0
ACUTE URANIUM EXPOSURE STANDARDS FOR WORKERS

Prepared by
Division of Fuel Cycle Safety, Safeguards, and Environmental Review
Office of Nuclear Material Safety and Safeguards

A. Introduction

This interim staff guidance identifies acute uranium intake quantities that the staff finds acceptable as proposed quantitative standards used to classify the chemical (i.e., nonradiological) consequences of worker acute uranium exposure accidents analyzed in licensee's or applicant's Integrated Safety Analysis (ISA) which is an essential element of the safety program required by Title 10 of the *Code of Federal Regulations* (10 CFR) Section 70.62. These standards are required by Subpart H, "Additional Requirements for Certain Licensees Authorized To Possess a Critical Mass of Special Nuclear Material," of 10 CFR Part 70, "Domestic Licensing of Special Nuclear Material."

This guidance may be used when evaluating licensee- or applicant-proposed quantitative standards for categorizing an acute uranium exposure event when such an exposure event is established as credible in an ISA. The licensee- or applicant-proposed quantitative standards are required by 10 CFR Paragraph 70.65(b)(7) as an element of an ISA summary and support the demonstration of compliance with the performance requirements of 70.61(b)(4) and (c)(4).

B. Discussion

The 2013 *Toxicological Profile for Uranium* issued by the Agency for Toxic Substances and Disease Registry (ATSDR), which is part of the U.S. Department of Health and Human Services, provides an overview of uranium toxicity and a summary of the information that supports the agency's assessment of uranium toxicity (ATSDR, 2013). This ATSDR document notes that no human fatalities have been reported as a result of uranium toxicity. It also includes a discussion of uranium transport through the body describing how uranium can enter the body through multiple routes of exposure (e.g., inhalation, ingestion) with most of the inhaled and ingested uranium leaving the body in the feces. The ATSDR document also points out that the fraction of the uranium that is absorbed into body fluids leaves the body through the urine, potentially causing damage to the kidney tubular cells as it exits the body. Any damage caused to the critical organ, the kidney, following an acute uranium exposure event depends on the mass of uranium that enters the body, the route of exposure (e.g., inhalation, ingestion), and the chemical form of uranium. Inhalation exposure results in a higher fraction of uranium adsorption into the body fluids and, therefore, results in more damage to the kidney than does the ingestion of the same amount of the same uranium compound. A higher fraction of more

soluble uranium compounds (e.g., uranyl nitrate, uranium hexafluoride) is absorbed into the body fluids and, therefore, results in more damage to the kidney than does an intake of the same mass of a less soluble uranium compound (e.g., uranium oxide).

Determining the acute uranium intake quantities that would be acceptable for use as a "proposed quantitative standard" as required by 10 CFR 70.65(b)(7) and consistent with the definition of high and intermediate acute chemical exposure consequences established in 10 CFR 70.61(b)(4) and (c)(4) requires a detailed review of uranium toxicity information, particularly information on intakes that are expected to result in effects that approximate the effects identified in 10 CFR 70.61(b)(4) and (c)(4). These are (1) life endangerment or (2) irreversible or other serious, long-lasting effects.

Information on uranium intakes that produce effects that approximate the high and intermediate consequence events defined in 10 CFR 70.61, "Performance Requirements," is sparse. The Royal Society (Royal Society, 2002) and U.S. Army (U.S. Army, 2004) have reviewed and analyzed the limited uranium exposure information and developed information on the relationship between uranium concentrations in the kidney and effects on the kidney. The Royal Society studies primarily used biokinetic models based on the following International Commission on Radiological Protection (ICRP) publications to estimate the uranium intake and peak renal concentration associated with 14 historical exposure events:

- Publication 66 (ICRP 1994a), "Human Respiratory Tract Model for Radiological Protection"

- Publication 69 (ICRP 1995), "Age-Dependent Doses to Members of the Public from Intake of Radionuclides—Part 3 Ingestion Dose Coefficients"

- Publication 78 (ICRP 1997), "Individual Monitoring for Internal Exposure of Workers"

The Royal Society studies proceeded to investigate the relationship between the predicted peak renal concentration and observed physiological kidney effects. This approach of using biokinetic models to estimate peak renal concentration allowed the investigators to use data from uranium exposure events that involved different exposure routes and different uranium compounds as they developed their understanding of the relationship between peak renal concentration and physiological effects on the kidney.

The Royal Society analysis concluded that renal concentrations greater than about 50μg (microgram) uranium per gram kidney (μg U/g kidney) are likely to lead to acute kidney failure that would be lethal in the absence of appropriate medical intervention.

The sparse information on human exposure events that result in noticeable health effects was re-examined by the U.S. Army. The U.S. Army effort reviewed the 14 cases analyzed by the

Royal Society, along with 13 additional cases described by Fisher, et. al. (Fisher 1990). The U.S. Army used this information to develop a range of relationships between renal concentration and physiological effects (referred to as renal effects groups). The information was presented and discussed in the 2004 U.S. Army report, "Depleted Uranium Aerosol Doses and Risks: Summary of U.S. Assessments." The National Research Council documented its review of these U.S. Army renal effects groups in its 2008 report, "Review of Toxicologic and Radiologic Risks to Military Personnel from Exposure to Depleted Uranium During and After Combat." The National Research Council committee endorsed the renal effects groups for the highest renal concentrations, the relationships that are considered most relevant for this effort.

The U.S. Army's highest renal effects group associated a renal concentration of greater than 18 μg U/g kidney with "possible severe clinical symptoms of renal dysfunction" and the predicted outcome of "likely to become ill." The next highest renal effects group associated a renal concentration of 6.4 to 18 μg uranium per gram kidney with "possible protracted indicators of renal dysfunction" and the predicted outcome of "may become ill."

The specific uranium exposure events analyzed by the Royal Society and the U.S. Army are summarized in Table 1. The table shows the different exposure events considered by the Royal Society and U.S. Army studies. The table shows that when both organizations examined the same exposure events, they had similar estimates of intake and peak renal concentration and similar characterization of renal effect severity.

Figure 1 shows a graphical presentation of this information and lists acute uranium intake and renal concentration estimates for the various reconstructed exposure events. The right side of the figure shows the renal physiological effects, including the Royal Society estimate of 50 μg U/g kidney that would lead to acute kidney failure and would be lethal without appropriate medical intervention, as well as the two upper renal effects groups identified by the U.S. Army and endorsed by the National Research Council. The figure also illustrates the limited data that supports these higher physiological effects estimates.

The staff compared the definition of high and intermediate consequence exposure events in 10 CFR 70.61 with the phrases reported by the Royal Society and the U.S. Army for relevant renal concentration ranges. The first comparison was for a high consequence exposure event, which is defined in 10 CFR 70.61(b)(4) with the phrase, "could endanger the life of a worker." The staff determined that this effect is slightly less severe than the effect the Royal Society associates with a renal concentration of greater than 50 μg U/g kidney, which is characterized by the phrase, "likely to lead to acute kidney failure that would be lethal in the absence of appropriate medical intervention." The staff concluded that a renal concentration of approximately 50 μg U/g kidney or more would result in a high consequence exposure event as defined in 10 CFR 70.61(b)(4), but the staff also considers there to be limited conservatism in this conclusion.

The second phrase the staff compared was for an intermediate consequence exposure event, which is defined in 10 CFR 70.61(c)(4) as "could lead to irreversible or other serious, long-lasting effect." The staff concluded that this effect is more severe than the effect that the U.S. Army associates with Renal Effect 3, greater than 18 µg U/g kidney. The U.S. Army characterizes the effects of this level of exposure with the phrases, "possible severe clinical symptoms of renal dysfunction, may become ill." Based on the available information, the staff concluded that a renal concentration of 18 µg U/g kidney could conservatively be described as an intermediate consequence exposure event. This position is supported by the U.S. Army study, which reported that the available uranium toxicity information suggests that acute renal toxicity from uranium does not necessarily lead to chronic toxicity, and by the National Research Council, which concluded that the question of whether uranium exposure can cause chronic or irreversible renal disease is still open.

The staff developed estimates of uranium intake quantities that would result in kidney uranium concentrations of 50 µg U/g kidney and 18 µg U/g kidney by using conversion factors derived from the current ICRP biokinetic models for uranium (Leggett, et. al., 2012). The biokinetic models used in developing the conversion factors were ICRP Publication 66 (1994a), ICRP Publication 100 (2006), "Human Alimentary Tract Model for Radiological Protection," ICRP Publication 68 (1994b), and ICRP 69 (1995). The conversion factors are based on conservative assumptions about uranium intake methods (i.e., inhalation) and uranium solubility class (i.e., Type F)[1]. Using the conversion factors, the uranium intake quantity associated with a renal concentration of 50 µg U/g kidney is 480 milligrams (mg) of Type F uranium and the uranium intake quantity associated with a renal concentration of 18 µg U/g kidney is 173 mg of Type F uranium.

The staff reduced the calculated value of 480 mg to the round number of 400 mg to account for the differences between the terms of 10 CFR 70.61(b)(4)(i) and the Royal Society characterization of the effects following an exposure that resulted in a renal concentration of greater than 50 µg U/g kidney, which was considered to be slightly more severe than the effects escribed in 10 CFR 70.61(b)(4)(i). The limited number of historical exposure events that have resulted in renal concentrations near 50 µg U/g kidney supports the staff's conservatism in developing an acceptable quantitative standard for a high consequence event as defined in 10 CFR 70.61. The 173 mg value was rounded down to 150 mg, consistent with the precision of the underlying information. As a result, an intake of 400 mg was identified as a quantity that would be acceptable for defining a "high" consequence acute uranium exposure event for a worker and an intake of more than 150 mg (but less than 400 mg) would be acceptable for defining an "intermediate" consequence acute uranium exposure event for a worker.

[1] Biokinetic models allow for three generic absorption types in their analysis: Type F, representing fast dissolution and a high level of adsorption to blood; Type M, representing a moderate rate of dissolution and an intermediate level of absorption to blood; and Type S, representing slow dissolution and a low level of adsorption to the blood (Leggett, el. al., 2012).

C. Regulatory Basis

According to 10 CFR 70.65(b)(7), ISA summaries are required to include a description of the proposed quantitative standards used to assess the consequences to an individual from acute chemical exposure to licensed material or chemicals produced from licensed materials.

D. Technical Review Guidance

The staff will accept the use of 400 mg as an acute intake quantity standard for a high consequence event for a worker and 150 mg as an acute intake quantity standard for an intermediate consequence event for a worker.

These uranium intake values were developed from specific renal concentrations of uranium based on assumptions about the nature of uranium intake (i.e., inhalation) and the solubility class of the uranium (i.e., Type F) and a renal concentration of less than 50 μg U/g of kidney for a high consequence event and a renal concentration of less than 18 μg U/g of kidney for an intermediate consequence event. The staff may accept other acute uranium intake values based on other assumptions if the assumptions are justified.

E. Recommendation

This ISG should be used as an addendum to NUREG-1520, "Standard Review Plan for the Review of a License Application for a Fuel Cycle Facility," to supplement information in Section A.2.

F. References

Agency for Toxic Substances and Disease Registry, "Toxicological Profile for Uranium," February 2013.

Fisher, D.R, M.J. Swint, and R.L. Kathren, "Evaluation of Health Effects in Sequoyah Fuels Corporation Workers from Accidental Exposure to Uranium Hexafluoride," NUREG/CR-5566, United States Nuclear Regulatory Commission, Washington D.C., May 1990.

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Leggett, R.W., et. al., “Controlling Intake of Uranium in the Workplace: Applications of Biokinetic Modeling and Occupation Monitoring Data,” Oak Ridge National Laboratory, TM-2012/14, January 2012.

National Research Council, Committee on Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat, Committee on Toxicology, “Review of Toxicologic and Radiologic Risks to Military Personnel from Exposure to Depleted Uranium During and After Combat,” 2008.

Nuclear Energy Institute, “Acute Chemical Toxicity of Uranium with Application to 10 CFR 70.61,” Revision 1, Ronald L. Kathren, the Kathren Group, Inc., May 22, 2009 (Agencywide Documents Access and Management System Accession No. ML091490747).

Royal Society, “The health hazards of depleted uranium munitions: Part II,” 2002.

U.S. Army, “Depleted Uranium Aerosol Doses and Risks: Summary of U.S. Assessments,” Attachment 3, “Human Health Risk Assessment of Capstone Depleted Uranium Aerosols,” October 2004.

Table 1 Acute Uranium Exposure Events Analyzed in Developing Relationship between Peak Renal Concentration and Renal Effects

				Royal Society			U.S. Army		
Reference	Intake route	Uranium form	Subjects	Intake, mg	Peak renal concentration µg U/g kidney	Effect severity	Intake, mg	Peak renal concentration µg U/g kidney	Effect severity
Pavlakis, et al, 1996	ingestion	acetate	1	8500	100	+++	8500	100	+++
Zhao and Zhao, 1990	dermal (burn)	nitrate	1	130	35	+++	130	35	+++
Zhao and Zhao, 1990	inhalation	UF4	1	900	10	++	920	10	++
Luessenhop et al, 1958	injection	nitrate	2	10	5	++	16 11	6 4	+ +
Butterworth, 1955	dermal (burn)	nitrate	1	10	3	++	10	3	++
Boback, 1975	inhalation	Ore concentrate	1	200	3	-			
Luessenhop et al, 1958	injection	nitrate	3	5	2	+	5.9 5.5 4.3	2 2 1.5	+ - -
Kathren and Moore, 1986	inhalation	UF6	3	50-100	1-3	+	40-50	4 4 1.2	+ + +
Butterworth, 1955	ingestion	nitrate	1	470	1	+	470	1	+
Boback, 1975	inhalation	UF6	1	20	1	-	20	1	-
Fisher et al, 1990	inhalation	UF6	13				24 18 18 17 15 12 11 11 8.7 8.4 7.4 6 6	2.5 1.9 1.9 1.8 1.5 1.2 1.1 1.1 0.9 0.87 0.76 0.62 0.62	+ - - - - - - - - - - - -

Effect severity code: +++ = clinical symptoms severe renal dysfunction, ++ = biochemical indicators of protracted renal dysfunction, + = biochemical indicators of transient renal dysfunction, - = no detectable effects

References cited in Table 1

Boback, Michael W., "A Review of Uranium Excretion and Clinical Urinalysis Data in Accidental Exposure Cases", Conference on Occupational Health Experience with Uranium, April 28-30, 1975, ERDA-93

Butterworth, A., "The Significance and Value of Uranium in Urine Analysis," Transactions of the Association of Industrial Medical Officers, 5, pages 36-43, 1955.

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Kathren R.L. and R.H. Moore, "Acute Accidental Inhalation of U: 38-Year Follow-Up," *Health Physics*, Vol. 51, No 5 (November), pp. 609-619, 1986.

Luessenhop, A.J., et. al., "The Toxicity in Man of Hexavalent Uranium Following Intravenous Administration", *The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine,* Volume 79, pages 53-100, 1958

Pavlakis, Nicholas, Carol A. Pollock, Greg McLean, and Roger Bartop, "Deliberate Overdose of Uranium: Toxicity and Treatment," Nephron, 72:313-317, 1996.

Zhao, Su Lu and Fu-Yao, "Nephrotoxic Limit and Annual Limit on Intake for Natural U," Health Physics, Volume 58, No. 5 (May) pages 619-623, 1990.

Figure 1 - Relationships between uranium intake (mass, form and route) and peak renal concentration and between peak renal concentation and renal effects