

# INPLASY PROTOCOL

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**Corresponding author:**  
Andrew Horvit

andrew.m.horvit@uth.tmc.edu

**Author Affiliation:**  
McGovern Medical School,  
UTHealth, The University of  
Texas at Houston HSC.

**Support:** N/A.

**Review Stage at time of this submission:** Data analysis.

**Conflicts of interest:**  
None declared.

## A Systematic Review and Meta-Analysis of Mortality and Kidney Function in Uranium – Exposed Individuals

Horvit, A<sup>1</sup>; Molony, D<sup>2</sup>.

**Review question / Objective:** 1) In humans, how does environmental and/or occupational exposure to uranium affect the risk of mortality due to primary kidney disease compared to unexposed individuals? (2) In humans, how does environmental and/or occupational exposure to uranium affect the risk of developing kidney failure compared to unexposed individuals?

**Eligibility criteria:** We included cohort studies that evaluate the risk of CKD/ESKD due to uranium exposure. We also included cohort studies that evaluate standardized mortality due to all-cause mortality, kidney cancer, chronic kidney disease, diabetes, and cardiovascular disease in humans with exposure to uranium. We also included cross sectional studies that evaluate renal function in humans exposed to uranium via biomarkers and hard clinical measures (such as creatinine clearance) compared to humans with low/no uranium exposure. In order to not include the same cohort multiple times in the statistical analyses, we selected studies that evaluated an outcome of interest for a given cohort for the longest follow-up period. When this was not possible (due to multiple studies using different combinations of cohorts with varying lengths of follow up), the study with the largest study population size was selected.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 April 2022 and was last updated on 19 April 2022 (registration number INPLASY202240122).

### INTRODUCTION

**Review question / Objective:** 1) In humans, how does environmental and/or occupational exposure to uranium affect

the risk of mortality due to primary kidney disease compared to unexposed individuals? (2) In humans, how does environmental and/or occupational exposure to uranium affect the risk of

developing kidney failure compared to unexposed individuals?

**Condition being studied:** Metal-related kidney toxicity, chronic kidney disease, ESKD, kidney cancer.

## METHODS

**Search strategy:** Databases: PubMed, Embase, Web of Science, TRIP; Search queries: Keyword searches: uranium kidney, uranium renal human, uranium kidney cancer human, uranium kidney failure human, uranium renal failure human, uranium nephritis, and uranium AND (SMR OR Standardized Mortality); MeSH term searches in Pubmed: {"Uranium/adverse effects"[Mesh] OR "Uranium/poisoning"[Mesh] OR "Uranium/radiation effects"[Mesh] OR "Uranium/toxicity"[Mesh] ) AND ("Kidney/adverse effects"[Mesh] OR "Kidney/radiation effects"[Mesh] OR "Kidney/toxicity"[Mesh] OR "Kidney Neoplasms"[Mesh] OR "Acute Kidney Injury"[Mesh] OR "Kidney Tubules, Proximal"[Mesh])} AND "Humans"[Mesh]} and {"(("Uranium"[Mesh] OR "Uranium/adverse effects"[Mesh] OR "Uranium/poisoning"[Mesh] OR "Uranium/radiation effects"[Mesh] OR "Uranium/toxicity"[Mesh] ) AND ("Kidney"[Mesh] OR "Kidney/adverse effects"[Mesh] OR "Kidney/radiation effects"[Mesh] OR "Kidney/toxicity"[Mesh] OR "Kidney Neoplasms"[Mesh] OR "Acute Kidney Injury"[Mesh] OR "Kidney Tubules, Proximal"[Mesh])) AND "Humans"[Mesh]}.

**Participant or population:** Humans of any age with known/suspected exposure to uranium.

**Intervention:** Exposure to uranium in occupational settings (such as miners, millers, and nuclear factory workers) and in the community (such as via water, air, food, soil).

**Comparator:** Humans in the same community/environment that did not have uranium exposure or population-level estimates derived from humans in the same state/nation.

**Study designs to be included:** Cohort studies, cross sectional studies.

**Eligibility criteria:** We included cohort studies that evaluate the risk of CKD/ESKD due to uranium exposure. We also included cohort studies that evaluate standardized mortality due to all-cause mortality, kidney cancer, chronic kidney disease, diabetes, and cardiovascular disease in humans with exposure to uranium. We also included cross sectional studies that evaluate renal function in humans exposed to uranium via biomarkers and hard clinical measures (such as creatinine clearance) compared to humans with low/no uranium exposure. In order to not include the same cohort multiple times in the statistical analyses, we selected studies that evaluated an outcome of interest for a given cohort for the longest follow-up period. When this was not possible (due to multiple studies using different combinations of cohorts with varying lengths of follow up), the study with the largest study population size was selected.

**Information sources:** PubMed, Embase, Web of Science, TRIP.

**Main outcome(s):** Risk ratio for developing ESKD/CKD; risk ratio for ESKD on renal replacement therapy; standardized mortality due to kidney cancer and chronic kidney disease; creatinine clearance in patients with uranium exposure compared to those without uranium exposure.

**Additional outcome(s):** Standardized mortality due to all cause mortality, diabetes, and cardiovascular disease; proteinuria, urine BMG, and urine NAG in patients with uranium exposure compared to those without uranium exposure.

**Data management:** Study selection: 2 reviewers applied the eligibility criteria for study selection. Upon completion of the literature searches, duplicates were removed and abstracts will be screened for inclusion. Studies that met the inclusion criteria were evaluated for inclusion in the final analysis through in depth examination of full length versions. Disagreements

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about study inclusion were resolved via discussion. **Data Extraction:** Data extraction was performed by the lead investigator. Data extraction was repeated twice to ensure accuracy of extraction. Differences in data extraction between the two attempts were resolved and checked a third time for confirmation of resolution. Demographic information about the populations under investigation (such as location of cohort, type of uranium exposure, comparator group, gender breakdown, length of follow up, loss to follow up), risk data, mortality data, and biomarker data was retrieved from the full length articles and stored in a Microsoft Excel spreadsheet.

#### **Quality assessment / Risk of bias analysis:**

Two reviewers assessed Risk of Bias; Newcastle Ottawa Scale was used to assess for Risk of Bias for cohort studies; The AXIS tool was used to assess for Risk of Bias for cross sectional studies. Disagreements were resolved through discussion between the two reviewers.

**Strategy of data synthesis:** Data synthesis is being performed if at least 3 studies report the given outcome of interest for a given form of uranium exposure. Data synthesis is being performed using RevMan 5.4. For each of the included studies reporting risk ratios/standardized mortality ratios, risk ratios are being calculated from the reported number of occurrences of the outcome of interest and the expected number of outcomes derived from population-level data. The risk ratios from the individual studies are being weighted using the Maentel-Hanszel method to derive an overall risk ratio/standardized mortality ratio for a given cause of death. Since RevMan 5.4 does not allow non-integer values to be used with Maentel-Hanszel method, expected deaths are being rounded to the nearest whole number using conventional rounding standards. For each of the included studies reporting biomarker data, mean differences are being calculated between the exposure/control groups and Inverse Variance is being used to determine an overall mean difference for the given

biomarker being analyzed. Random Effect models are being used for all analyses.

**Subgroup analysis:** Subgroup analyses are being performed for the analyses. The subgroups will be based on type of uranium exposure (millers/miners vs nuclear factory workers vs military vs environmental).

**Sensitivity analysis:** The sensitivity analysis is performing analyses on all included studies that were that reported on any of the predetermined outcomes of interest (regardless of whether they reported renal outcomes) and comparing them to the analyses involving the subset of included studies that reported outcomes due to primary renal disease. This will help determine whether the subset of studies that report mortality due to primary renal disease have different characteristics from the overall collection of included studies.

**Language:** English.

**Country(ies) involved:** United States.

**Keywords:** Systematic review; Meta-analysis; Uranium; Kidney; Mortality; Kidney Failure.

#### **Contributions of each author:**

Author 1 - Andrew Horvit.

Email: andrew.m.horvit@uth.tmc.edu

Author 2 - Donald Molony.

Email: donald.a.molony@uth.tmc.edu