AMERICAN UNIVERSITY OF BEIRUT

A SYSTEMATIC REVIEW OF THE ASSOCIATIONS BETWEEN EXPOSURE TO WEAPONIZED URANIUM AND ADVERSE HEALTH OUTCOMES AMONG THE IRAQI POPULATION

by
SHELBY LOUISE SURDYK

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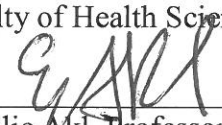

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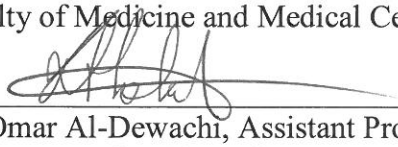

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AN ABSTRACT OF THE THESIS OF

Shelby Louise Surdyk for Master of Science in Environmental Sciences
Major: Environmental Health

Title: A systematic review of the associations between exposure to weaponized uranium and adverse health outcomes among the Iraqi population

Background. For decades, the literature has been wrought with disagreement over the health impacts of depleted uranium (DU) weapons. In a 2013 Lancet World Report, Paul C. Webster highlighted the need for a thorough review of the literature regarding the impact of war remnants – including DU – on the incidence of congenital birth defects in Iraq. To date, no systematic review on the topic has been undertaken. Thus, we aimed to critically appraise and systematically synthesize the evidence on adverse health outcomes associated with DU exposure among the Iraqi population.
Methods. We searched eleven academic and grey literature databases, without language restrictions. We included human observational comparative studies published between 1990-2018 that measured association between exposure to weaponized uranium and health outcomes (such as cancer, birth defects, immune system function, and mortality) among the Iraqi population. Studies were excluded based on population (non-Iraqi), exposure (did not assess uranium exposure), control (did not include a comparator population), outcome (did not report health outcomes), and study-design (did not contain original data or analysis). Using the Navigation Guide's risk of bias tool, internal validity was assessed for each included study. This study is registered with PROSPERO, number CRD42018108225.
Findings. Our searches identified 2,009 records, of which 21 met our inclusion criteria. We identified 5 additional records from other sources. As four articles reported the results of multiple relevant studies, our final set included 26 articles reporting 31 studies. Most of our included studies (n=25, 80.6%) reported finding a positive association between uranium exposure and adverse health outcomes. We found that the reviewed body of evidence suffers from a high risk of bias.
Interpretation. The available body of evidence suggests that DU weapons have impacted public health in Iraq. We call on the international community to support Iraqi scientists, whose capabilities have been undermined by war, economic sanctions, and an intellectual embargo, as they advance research on this topic.

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CHAPTER I

INTRODUCTION

"The Gulf War opened one of the most important debates on the relationship between public health, science, medicine, public opinion, media, and politics on the one hand and war (...) on the other."

- Slobodan Lang

1.1 Research Question

Is environmental exposure to weaponized uranium associated with adverse health outcomes among the Iraqi population?

1.2 Thesis Objectives

1) Identify and summarize the findings of all eligible human observational studies on the topic and evaluate the quality of evidence.
2) Identify gaps in the literature and future research needs.
3) Make recommendations for policy interventions based on study findings.

1.3 Thesis Significance

The value of this thesis comes from its potential to inform the following question: Is pollution from depleted uranium weapons causing death and disease in Iraq?

It is a deeply politicized, complex, and extremely important public health question to untangle. To answer it, as with any toxicological public health question, a large body of primary studies is needed, particularly with respect to establishing

causality. This thesis, a systematic review, will identify and synthesize the evidence from one stream of primary data: human observational studies. More specifically, it will systematically search for and appraise all human observational studies that have measured associations between exposure to weaponized uranium and patient-important health outcomes among the Iraqi population. While this approach cannot establish causality, it can speak to one piece of the causal puzzle and inform future investigations. This thesis is the first systematic review on the topic, and it is reported in accordance with PRISMA guidelines.

1.4 Thesis Organization

Chapter 2 (Background) will place the systematic review in context, as well as justify its relevance and methodology. To begin, the chemical and radiological features of uranium, a naturally occurring radioactive element, will be described. Second, the process of uranium enrichment and its use in nuclear technology (e.g. nuclear weapons and fuel for nuclear reactors) will be presented. Depleted uranium (DU) is a by-product of uranium enrichment, and this section will summarize the known production, storage, and use of DU in both civilian and military applications. The third section of Chapter 2 provides an in-depth case study of DU use and distribution in Iraq - from the first Gulf War (1991) to the present. Information on the amount and geographic extent of DU contamination in Iraq is necessary for constructing and understanding exposure scenarios faced by the Iraqi population. In order to establish a link between pollutant exposure and public health impacts in a population, the toxicokinetics of a pollutant must be understood. Therefore, a brief description of uranium metabolism, biokinetics, and mechanism of toxicity will be presented. The facts concerning DU's characteristics,

toxicity, and distribution in Iraq create the backdrop of a decades long debate over the impact of DU on public health in the country (Faa 2018). A discussion of this debate, and the controversies underlining it, will be provided in the fourth section of this chapter. A vast divide exists in the academic literature, and even between governmental reports, over whether associations exist between DU exposure and public health impacts in Iraq including birth defects, cancers, and infertility. Thus, Chapter 2 will conclude in its fifth section by emphasizing the need for a systematic review in order to assess and synthesize the body of evidence.

Chapter 3 (Methodology) provides a detailed, transparent, and reproducible protocol for our systematic review. It covers every aspect of the systematic review methodology, from forming a review team, to synthesizing the findings of our included studies. The intervening steps are as follows: developing a PECOS statement, selecting sources and developing a search strategy, implementing the search strategy and downloading all records captured, registering the systematic review protocol on PROSPERO, conducting calibration exercises to train reviewers and test agreement in eligibility screening, implementing the screening process following pre-specified guidelines, acquiring full texts, abstracting data from all included studies, and conducting a risk of bias assessment for all included studies. Explanations for specific decisions made during each step of the methodology are provided, with references to literature which justify those decisions.

Chapter 4 (Results) presents our PRISMA flow diagram for study inclusion. It summarizes the characteristics of included studies, as well as the findings of individual studies, and it presents the general findings across the body of evidence for each health outcome. Additionally, the results of risk of bias determinations are provided.

Chapter 5 (Discussion) critically appraises the findings of included studies, by outcome, in light of both study characteristics and risk of bias determinations. It summarizes the results of previous reviews concerning health impacts of depleted uranium in Iraq and places the findings of this systematic review in context. In the process, it elucidates the contribution that this systematic review has made to the literature. Building on the discussion of limitations of our included studies, Chapter 5 makes specific recommendations for future primary research (namely, human observational studies) that should be carried out in order to further clarify the possible health impacts that depleted uranium has had on the Iraqi population. Although the aim of this thesis is to assess the quality of evidence for an association between uranium exposure and adverse effects, this chapter will also review the Bradford Hill Criteria for causality (of which association is one element). A discussion of gaps in the literature with regard to each element will be provided.

Chapter 6 (Conclusions and Policy Recommendations) reiterates the main outcomes of this systematic review and places them into a policy context. Policy recommendations are made on both the national scale concerning health policy and interventions in Iraq, and on the international scale regarding the legality of DU weapons.

CHAPTER II

BACKGROUND

2.1 Properties and characteristics of Uranium

Depleted uranium is derived from, and is chemically identical to, elemental natural uranium. In this section the physical, chemical, and radiological properties of uranium will be presented. As such, it will also cover basic concepts of chemistry and radiation physics, which are fundamental to the understanding of uranium toxicity, including its chemical- and radiation-induced health effects (HHS 2013).

2.1.1 Physical characteristics

Uranium is an element in the actinide series (HHS 2013) and is one of the heaviest naturally occurring elements, second only to plutonium-244 (Hoffman and Politis 1979). In metallic form, it has a density of 19g/cm^3, which is nearly twice the density of lead (HHS 2013). To put this in perspective, a single liter (1000 cm^3) of uranium would weigh nearly 20 kg. Additionally, it has a low melting point (1,135 ºC), relative to other heavy metals such as tungsten (3,422 ºC) or titanium (1,668 ºC) (Lide 2005).

The atomic number of uranium is 92, and its atomic mass is 238.03 amu (1983). In nature, uranium exists in three isotopic forms: U-238, U-235, or U-234 (HHS 2013). The ratio (or relative abundance) of naturally-occurring uranium isotopes is consistent throughout the earth's crust and the heaviest naturally occurring isotope, U-238, is also the most abundant (see **Table 1**).

Table 1. Isotopic weights and relative abundance of natural uranium (Schön, Winkler et al. 2004)

Isotope	Number of protons	Number of Neutrons	Relative abundance	Mass (amu)
U-238	92	146	99.284%	238.0508
U-235	92	143	0.711%	235.0439
U-234	92	142	0.005%	234.0409
		Atomic weight of elemental uranium		238.03

Another notable characteristic of elemental (metallic) uranium is its pyrophoricity. Like some other metals, uranium is capable of spontaneously combusting at room temperature (the minimum ignition temperature is 20 °C) (Mackinson 1981). Exposed to air, small uranium metal particles (spherical diameter < 1.5 mm) will self-ignite and rapidly oxidize in an exothermic (heat producing) reaction (Peacock 1992). The surfaces of uranium metal shards and fragments with a spherical diameter larger than 1.5 mm will oxidize when exposed to air, but will not ignite under normal conditions (Peacock 1992).

2.1.2 Radioactive Properties

Physicist and historian, Dr. Spencer Weart, has argued that common misconceptions about the science of ionizing radiation have led to irrational public fears about the health risks posed by radioactive elements (Weart 2012). So, this section will outline the basic principles of radioactivity, in order to form the basis for a rational evaluation of uranium's radiotoxic properties.

Every element above bismuth (atomic number 83) on the Periodic Table, including uranium, possesses radioactive isotopes (OpenStax 2016). The reason for this

is that elements with a high atomic number possess extremely large nuclei, and the forces holding the nuclei together are weak (OpenStax 2016). Periodically, the forces will fail, and the large nuclei will break apart into smaller pieces in a process called nuclear decay (also called disintegration, transformation, or fission). Nuclear decay is a characteristic inherent to radionuclides (radioactive atoms) and occurs at a constant rate regardless of environmental factors such as pressure, temperature, acidity, etc. (HHS 2013). When a decay happens, a little bit of energy (radiation) is released from the broken nuclei. Sometimes, the smaller pieces of the broken nuclei (called decay daughters or progeny) are still too large to remain stable and will break apart again. The process of nuclear decay will continue until a small-enough, stable (nonradioactive) isotope, like lead (atomic number 82), is reached. Atoms of lighter elements (below bismuth) can also possess unstable nuclei (i.e. be radioactive) if they possess too few or too many neutrons (HHS 2013).

The primary type of radioactive energy emitted by uranium is alpha radiation (HHS 2013). Alpha radiation is one of many types of radiation that can be emitted during nuclear decay of radioactive elements. The other two types most relevant to environmental health are beta and gamma radiation (HHS 2013). Alpha radiation involves the emission of particles (essentially helium nuclei) that contain two protons, two neutrons, and possess a positive charge (Lawson 1999). Their large size (atomically speaking) and positive charge gives them a strong ability to cause biological damage, but also gives them the least penetrating power of any type of radiation (Lawson 1999). Their emission can be blocked by a thin piece of paper, and through air, alpha particles can only travel four centimeters (Lawson 1999). Beta radiation also involves the emission of particles (essentially identical to electrons) which possess a charge, can be

blocked by a thin piece of aluminum, and through air, can travel only one meter (Lawson 1999). Unlike alpha and beta radiation, gamma radiation does not involve the emission of particles, but rather the emission of electromagnetic energy, similar to x-rays, radiowaves, or visible light (HHS 2013). Although gamma radiation does not possess a charge (like alpha or beta particles) it has the greatest penetrating power of any type of radiation and can pass through one meter of concrete. Through air, gamma radiation can travel hundreds of meters (NRC 2017).

All uranium originally derives from supernova nucleosynthesis, and all naturally occurring U-238 and U-235 isotopes on earth (known as primordial isotopes) were formed during one or more supernovas that occurred approximately 6 billion years ago (Fairlie 2008). Because the isotopes are radioactive, all of the U-238 and U-235 isotopes on earth have been slowly decaying overtime, since the planet's formation. The U-238 isotope (again, the most abundant) decays progressively through 17 radioactive daughters until the stable isotope Pb-206 is reached **(Figure 1)** (Arazo, Barroso Mancha et al. 2016). This decay chain includes the production of the naturally occurring U-234 isotope. Concurrently, the U-235 decay chain includes 13 radioactive daughters, ending in the stable isotope Pb-207. Not all radionuclides decay by the same mode, rate, or type of energy emitted (as depicted in **Figure 1**). While U-238 atoms decay to Th-234 through the emission of an alpha particle, Th-234 decays to Pa-234 through the emission of a beta particle **(Figure 1).** The unique decay pathway for each uranium isotope demonstrates that, although all isotopes of uranium share the same chemical properties, their radioactive properties differ (HHS 2013).

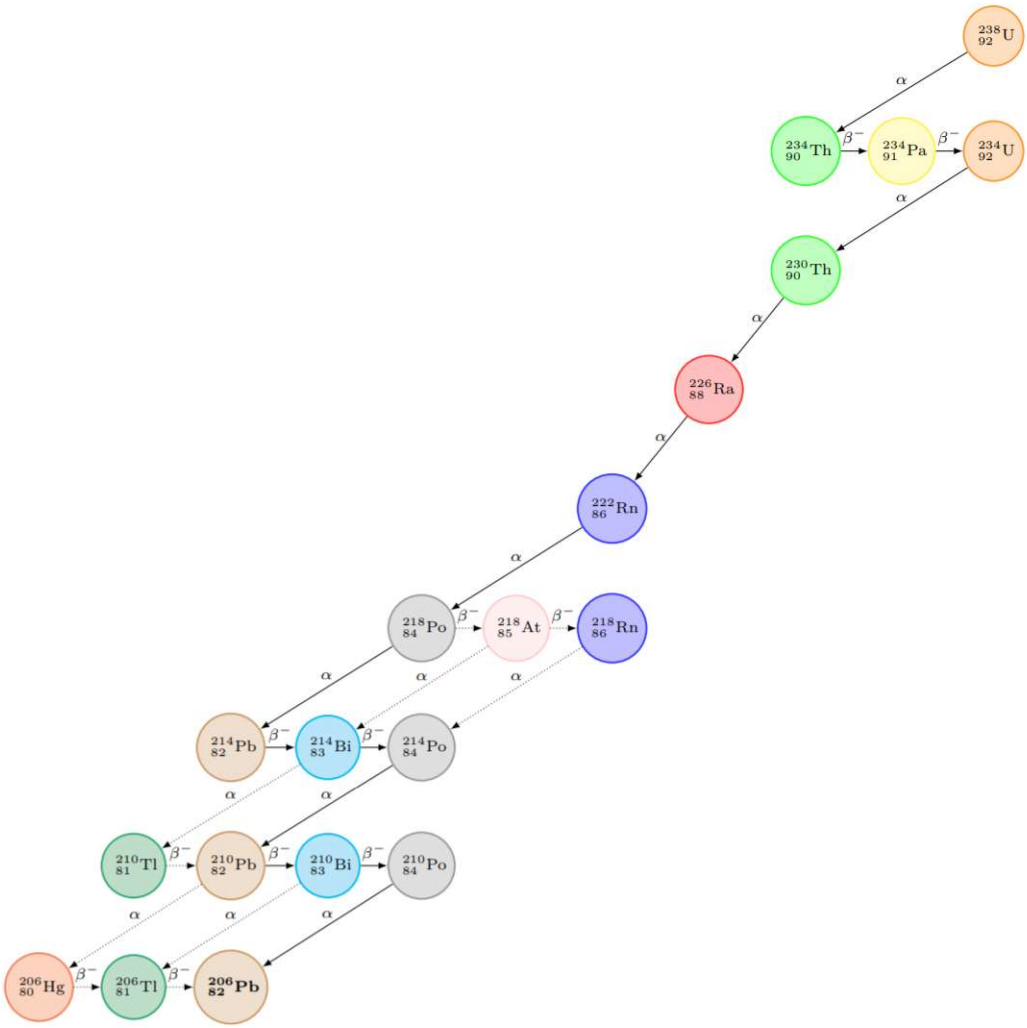

Figure 1. Uranium-238 decay chain (Source: Arazo et al, 2016)

Decay pathways for uranium isotopes are determinable, but the transformation of individual atoms is stochastic (i.e. random). Because the process of nuclear decay is random, the moment that an individual radionuclide will decay cannot, by definition, be predicted (HHS 2013). However, for a known volume of any specific type of radionuclide, it is possible to predict what percentage of the radioactive atoms will decay over a given time interval (HHS 2013). This is called the rate of decay.

For any radioactive substance, there are two ways by which the rate of decay is commonly reported: specific activity and half-life.

Activity is defined as the number of disintegrations (individual atoms which undergo nuclear decay) per unit time, whereas *specific activity* is defined as activity per unit mass or volume (HHS 2013). The SI unit for activity is the Becquerel (Bq), which is equivalent to one disintegration per second. With this information, one can say that the higher the specific activity of a radioactive material, the faster its rate of decay. Because radioactive decay chains eventually lead to the production of stable, nonradioactive isotopes, the specific activity of any given radioactive material (and its rate of decay) will decrease over time.

Radiological half-life is defined as the time that it takes for exactly half of the atoms of a pure radioactive substance of a given mass to decay. In other words, it is time that it takes for the activity of a radioactive material to decrease by half. Half-lives of specific radioisotopes are determined experimentally (Pommé 2015), and can vary widely between different radionuclide species. For example, Ra-226 has a half-life of 1600 years (Gorshkov, Gretchenko et al. 1961), whereas Po-218 has a half-life of only three minutes (Martz, Harris et al. 1989). Both Ra-226 and Po-218 are progeny in the U-238 decay chain (Arazo, Barroso Mancha et al. 2016). Each isotope of uranium has a unique half-life (as depicted in **Table 2**), and U-238, the heaviest and most abundant of the three naturally occurring isotopes, has the longest (approximately 4.5 billion years) (HHS 2013).

Contrary to popular belief, the length of a radioisotope's half-life does not necessarily indicate the level of radiological risk that it poses. Possessing a lengthier half-life means that U-238 has a lower specific activity and slower rate of decay than

either U-235 or U-234. Consequently, U-238 contributes less than half of the radiation dose received from exposure to natural uranium, although it makes up more than 99% of the mass of natural uranium by weight. In uranium with a natural isotopic ratio, U-238 contributes 48.8% of the total activity, while U-234 contributes an equal amount (48.8%), and U-235 contributes only 2.4% of the total activity (IAEA 2018) **(Table 2).**

Table 2. Relative isotopic abundance by weight and activity for natural uranium

Isotope	Relative abundance by weight	Relative abundance by activity	Activity (Bq/mg)	Half-life (years)
U-238	99.284%	48.8%	12.4	4,510,000,000
U-235	0.711%	2.4%	80	710,000,000
U-234	0.005%	48.8%	231,000	247,000
Total	100%	100%	**25.4**	

2.1.3 Form and Distribution in Nature

Weaponized uranium introduced to the environment via conventional weapons is not the only source of uranium exposure faced by the Iraqi population. This is a fact that must be taken into consideration when assessing uranium concentration in human biological samples and assessing the health risks posed.

Uranium is ubiquitous in the earth's crust and exists at an average concentration of 2.76 wppm (parts per million by weight) in all soil and rocks, making it equally as abundant as other common minerals such as tin (Herring 2012, Faa, Gerosa et al. 2018). The concentration of natural uranium in air averages about 1.3×10^{-7} mg/m^3 (NCRP 1999), while concentrations in surface and ground water typically vary from 0.003 to 2.1 μg/l (WHO 2001).

In their elemental form, uranium atoms (valence state 0) are highly reactive. So, in nature they do not exist as pure elemental metal, but rather as compounds and mineral ores (Bleise, Danesi et al. 2003). There are more than 100 types of uranium ores worldwide, (HHS 2013). Most ores of commercial interest have uranium concentrations of >1000 ppm (HHS 2013), and are primarily found in phosphate rock, lignite, and monazite sands (HHS 2013). According to the 26th edition of the Red Book, a biennial publication produced by the IAEA and the OECD, the total mass of identified (and economically attractive to extract) uranium metal globally is 5,718,400 tons (NEA 2016). Economically attractive uranium metal is that which is estimated to cost < $130/kg to extract (NEA 2016).

The quality, distribution, and concentration of uranium compounds and ores vary globally. While most uranium ores contain less than 5% uranium by weight (compared to the global average uranium concentration of 0.0004%), some deposits contain as much as 22% (HHS 2013, Faa, Gerosa et al. 2018). The IAEA reports that 75 countries in the world possess significant uranium ore deposits, of which Australia contains the largest fraction (Wang, Song et al. 2017). The Olympic Dam mine in southwest Australia is the world's single largest uranium deposit, representing almost one third (two million tons) of all uranium ore worldwide (Herring 2012). However, the country with the greatest amount of uranium production is Kazakhstan (Selvakumar, Ramadoss et al. 2018).

In nature, uranium exists in secular equilibrium with its decay daughters (Bleise, Danesi et al. 2003). Because of the long half-lives of uranium isotopes relative to the half-lives of their decay daughters, the total number of decay daughters will increase overtime, until the rate of decay daughters produced by the parent isotopes

equals the rate of decay of the daughters themselves. In order words, the activities of daughters become equal to the activity of the parent isotopes. This is called secular equilibrium.

Due to the phenomenon of secular equilibrium, natural uranium ores are far more radioactive than purified elemental uranium. Natural uranium ore, in secular equilibrium with its decay progeny, has four to five times the activity of isolated uranium (Bleise, Danesi et al. 2003). When uranium is isolated, the decay chain is broken, and only two daughters (thorium and protactinium) will again achieve secular equilibrium in a measurable timeframe after isolation (Bleise, Danesi et al. 2003). This point is also important to consider with regard to exposure assessments. Although radon and radium are decay daughters of uranium, their concentration in the environment will not be increased by the use of conventional uranium weapons. However, the concentrations of thorium and protactinium will be increased. Communication with Dr. Mozghan Savabieasfahani (University of Michigan), revealed that her research group is currently conducting a study into the associations between thorium exposure and adverse health effects in Iraq (to be published later this year).

2.1.4 Fission and uranium enrichment

This chapter has so far focused on the chemical and radiological properties of uranium, not depleted uranium. In this section, the production and origins of depleted uranium will be explained.

While all isotopes of uranium are radioactive and will undergo spontaneous fission reactions (albeit at very slow rates), not all are *fissionable*. To be fissionable, an isotope must undergo nuclear decay in response to a trigger, such as a neutron striking

the nucleus. In 1939, it was discovered that the nuclear decay of uranium atoms could be induced, artificially, by bombarding uranium nuclei with neutrons (Badash, Hodes et al. 1986). Three years later, Enrico Fermi at the University of Chicago applied that discovery to build mankind's first controlled nuclear chain reaction (Badash, Hodes et al. 1986). In his experiment, Fermi triggered the decay of uranium isotopes, which themselves in turn released energy, triggering the decay of other nearby isotopes, in a domino effect – a chain reaction. However, of the naturally occurring uranium isotopes, only U-235 is fissionable (i.e. will undergo a nuclear chain reaction), and Fermi's experiment, though effective, was inefficient. To work, it required a literal five ton "pile" of natural uranium (Badash, Hodes et al. 1986).

Conducted at the height of WWII, Fermi's experiment was seen to have immediate military applications (Badash, Hodes et al. 1986). While natural uranium contains a small percentage of U-235, Fermi's experiment confirmed that it does not contain enough to efficiently produce deliverable bombs. So following the experiment, scientists in America (specifically those enlisted into the Manhattan Project) urgently began research into the uranium enrichment – the process of filtering out less reactive U-238 isotopes from uranium, creating a product with an "enriched" ratio of U-235 isotopes (Badash, Hodes et al. 1986).

During the enrichment process (gaseous diffusion), uranium oxides obtained from the ore-milling process are first converted into uranium hexafluoride gas (UF_6). Then, the UF_6 is passed through a series of diffusion stages with progressively smaller holes (HHS 2013). Because U-235 and U-234 atoms are smaller and lighter that U-238, the UF_6 at the downstream end of diffusion system will have an enriched proportion of

U-235 atoms compared to natural uranium, while the upstream end will have a depleted proportion (HHS 2013).

Today, uranium is enriched for both nuclear weapons material and civilian nuclear reactor fuel. While uranium produced for nuclear weapons or nuclear submarine fuel can be enriched as high as 97% U-235, uranium fuel for commercial nuclear energy is typically enriched to only 3-4% U-235 (compared to the natural relative abundance of U-235 of 0.7%) (HHS 2013). The total amount natural uranium needed annually to produce fuel for the world's 435 reactors is 66,000 tons (Herring 2012).

2.2 Depleted uranium: Properties and production

When uranium is enriched for civilian or military purposes, a waste product with a smaller proportion of U-235 and U-234 isotopes is produced: depleted uranium. Because most of the radioactivity of uranium derives from U-235 and U-234 isotopes, depleted uranium is 40% less radioactive than natural uranium. Typically, 5 kg of DU is generated per 1 kg of enriched uranium (Jiang and Aschner 2015). As of 2012, there was approximately one million tons of depleted uranium stored globally in the form of uranium hexafluoride (UF_6) (IARC, 100D, 2012). While (depleted) uranium hexafluoride has few direct commercial uses, it can be processed into pure, elemental uranium metal, which has a variety of civilian and military applications.

2.2.1 Civilian uses of depleted uranium

Due to its extreme density, DU metal's most common civilian use is as a counter weight or ballast in planes, ships, and satellites. In the mid-1990's, the Boeing Corporation had approximately 15,000 DU weights in use in its civilian Boeing-747

fleet but has since began replacing DU weights with Tungsten (Betti 2003). Infamously, a Boeing-747 (with nearly 300kg in DU counter-weights) crashed in Amsterdam in October 1992 (Betti 2003). One-hundred and fifty-two (152) kg of depleted uranium was unaccounted for in clean-up operations and was likely oxidized during the crash and explosive fire. Another Boeing-747 carrying 425kg in DU counter-weights crashed in England in January 2000 (Betti 2003). These high-profile accidents and public backlash over fears of DU exposure prompted Boeing to begin replacing DU with Tungsten in counter-weights, but it is unknown how many DU counter-weights are in use in Boeing aircraft today (Boin, Van Duin et al. 2001).

Another important civil use of DU is in radiation shielding. The density of DU makes it the most efficient material for blocking high-penetrating gamma-rays, and because DU is categorized as a low-level radioactive material, it is considered safe for use in radiation shielding during transport of highly radioactive material (Betti 2003). As a waste material from uranium enrichment, DU's abundance and low cost make it an economically attractive alternative to other metals or concrete. For example, DUCRETE is a trade-marked material used in the construction of transportation and holding facilities of spent nuclear fuel (Khelurkar, Shah et al. 2015). Additionally, DU has been used as radiation shielding in some medical and research settings.

2.2.2 Military uses of depleted uranium

The volume of DU used for military purposes is thought to far exceed that used in civilian applications. According to the International Coalition to Ban Uranium Weapons, at least 20 countries possess DU weapons in their military stockpiles **(Table 3).** The US military is believed to possess the largest arsenal of DU munitions and

equipment, followed by the UK and France, but data has not been published on the exact (or even estimated) sizes of DU arsenals of any country. A report by the authoritative Jane's Armor and Artillery listed the sales of some DU tank munitions from the US to other countries in 1999 **(Table 3).**

Table 3. List of countries possessing DU weapons

Country	Size of DU arsenal
Azerbaijan	-
Bahrain	-
Belarus	-
China	-
Egypt	10,800 M1A1 rounds (120 mm), US export (Mannes 2002)
France	-
Georgia	-
Greece	-
Kazakhstan	-
Kyrgyzstan	-
India	-
Israel	300 M833 rounds (120 mm), US export (Foss 1999)
Jordan	2,130 M833 rounds (120 mm), US export (Foss 1999)
Pakistan	10,025 M833 rounds (120 mm), US export (Foss 1999)
Russia	-
Saudi Arabia	320 M833 rounds (120 mm), US export (Foss 1999)
Taiwan, Province of China	1,000 M774 rounds (105 mm), US export (Foss 1999)
Tajikistan	-
Turkey	84,451 M774 rounds (105 mm), US export 22,920 M833 rounds (120 mm), US export (Foss 1999)
Turkmenistan	-
Ukraine	-
United Kingdom	-
United States	-
Uzbekistan	-

* Countries for which arsenal size and DU weapons imports are not known are designated with "-".

There are three ways in which DU is used in military equipment and conventional weapons. First, as armor plating in tanks and heavily-armored vehicles (such as the Bradley Fighting vehicle). Second, in anti-tank penetrators and incendiary munitions. Third, in 20mm bullets for mounted artillery (Fahey 2004, Zwijnenburg 2013).

To date, only three countries have admitted to deploying DU weapons in war: the US, the UK, and Israel. Although the US began to develop and experimentally test DU weapons as early as the 1950's, the first reported use of DU weapons in a military conflict was not until 1985, when an Israel gunship shot and sank a boat off the Israel coast using DU rounds (Fahey 2004). The first widespread use of DU in an armed conflict was not until the first Gulf War in 1991 (Okafor-Yarwood 2014). Since then, (US manufactured and supplied) DU weapons have been used in at least five countries during the Yugoslav Wars in the Balkans (Croatia, Montenegro, Kosovo, Serbia, and Bosnia and Herzegovina). In 2017, it was also revealed that the US has used DU munitions in Syria (Oakford 2017). The use of DU weapons in Lebanon (by Israel) and Afghanistan (by the US) has been speculated, but not confirmed, and data regarding the detection of DU in warzones in those two countries remain controversial (Fahey 2004). Some sources have asserted that DU weapons were used by Israel during the 1973 Arab-Israeli War (Al Ani and Baker 2009). However, no independent research has verified those claims.

2.3 Depleted uranium in Iraq: Amount and distribution

2.3.1 First Gulf War

In order to contextualize the use of DU in Iraq, and the politization surrounding it use, this section will provide a brief introduction into US involvement in the first Gulf War. It will also summarize the amount and geographic distribution of DU introduced to the Iraqi environment during the first Gulf War, to the extent that it is known.

The first US Gulf War began in January 1991, a few months after Saddam Hussein invaded Kuwait (Taylor 2016). Within hours of the invasion on August 2nd, 1990, the UN Security Council issued resolution 660, calling for Iraq to retreat (Gordon 2010). After a series of UN resolutions and diplomatic talks had failed to catalyze Iraq's withdrawal from Kuwait, the UN Security Council passed resolution 678 which set a deadline for Iraqi withdrawal by January 15th, 1991 (Gordon 2010). The deadline passed, and the US launched an air assault on Iraq the following day. The US air campaign, code-named Operation Desert Storm, lasted 42 days and is considered one of the most intensive air campaigns in military history (Tilford 1993). It was accompanied simultaneously by a 100-hour ground assault (launched in February 1991), carried out and co-financed by a coalition of 30 countries (USDOS N.D.).

At the time of the first Gulf War, the Iraqi army was the fourth strongest in the world. In addition to a troop force of nearly 1,000,000 soldiers, and reserve force of more than 500,000, Iraq possessed a tank fleet of 4,500 tanks – purchased with loans provided to Iraq by Kuwait and Saudi Arabia during the Iran-Iraq War of the 1980's (Corvisirer and Childs 1994). In preparation for a confrontation against Iraq's impressively armed and armored tanks, the US added DU rounds to its deployed

arsenal. In fact, the first Gulf War came to include the largest tank battles in US history (Corvisirer and Childs 1994).

Overall, more than 90,000 tons of bombs were dropped on Iraq during the first Gulf War (Dewachi 2017). According to a report released by the US Army Environmental Policy Institute in 1995, that figure included 350 tons of DU (more than 300,000 kilograms), dispersed over an area of 20,000 square kilometers in Iraq, as well as battle sites near the Iraqi borders in Saudi Arabia and Kuwait (USAEPI 1995). Additionally, the UK military reported using 408 kilograms of DU weapons during the first Gulf War (Zwijnenburg 2013).

During the war, the US fired DU munitions from both jets and tanks, but the vast majority (>80%) were fired from A-10 Warthog fighter jets (Zwijnenburg 2013). By conservative estimates, A-10's alone destroyed 987 Iraqi tanks, including approximately 100 that were specifically targeted with DU munitions (Zwijnenburg 2013). All of the DU munitions used by the British military during the first Gulf War were fired from Challenger tanks (Zwijnenburg 2013).

Geographic data concerning the use of DU weapons during the first Gulf War is scarce; only a crude, low-resolution map depicting the sites of seventeen major tanks battles in Kuwait and Southern Iraq where DU weapons were used has been released by the US military (Zwijnenburg 2013). The map also includes general zones where 30mm caliber munitions were fired from air-sorties, possibly including DU munitions. More comprehensively, the Iraqi Radiation Protection Center (RPC) (established in 2003), has also sought to assemble geographic information on DU-impacted sites in Iraq, based on known locations of tank battles, as well as areas that have been surveyed radiometrically (Zwijnenburg 2013). While the RPC's data is more extensive and

detailed than the map released by the US military, it cannot be said to be completely comprehensive. It, too, identifies only sites in the Basrah governorate that were impacted by DU during the first Gulf War.

2.3.2. US invasion and occupation (2003)

Unlike after the first Gulf War, the US military has not released official estimates on the total amount of DU weapons used in Iraq since the 2003 invasion. Conversely, the UK *has* released official estimates on the amount of DU used in Iraq during the 2003 invasion: 870 kilograms – twice as much as was deployed by the UK during the first Gulf War (Zwijnenburg 2013). In 2010, the International Atomic Energy Agency estimated that the total amount used by the US in Iraq since 2003 could be as much as 1700 tons (>1.5 million kilograms) (IAEA 2010). Using satellite imagery, UNEP has estimated that as much as 2000 tons (1.8 million kilograms) of DU was used in Iraq between 2003-2011 (Zwijnenburg 2013). That's equivalent to 4 kilograms of DU per square kilometer in Iraq. In the time since those estimates, the US has continued to use DU weapons in military offensives against the Islamic State in Iraq (Oakford 2017).

Outside of the total amount used, the deployment of DU munitions in the 2003 Iraq War differs from the first Gulf War in two important ways: in geographic scope and in types of targets selected. While the extent of DU-impacted sites in Iraq during the first Gulf War was, by all available evidence, restricted to the governorate of Basrah, the RPC has documented sites contaminated with DU from the 2003 invasion throughout Southern Iraq (including the governorates of Dhi-Qar and Muthanna), as well as in Baghdad, Fallujah, and Al-Zubayr (Al-Azzawi 2006, IAEA 2010).

Investigative research by Wim Zwijnenburg from the Norwegian peace organization IKVPAX Christi has also confirmed the use of DU weapons in Najaf, Karbala, Al-Samawa, and Nasiriyrah during the 2003 Iraq War (Zwijnenburg 2013). In the course of his research, Zwijnenburg made three visits to Iraq, and traveled to sites where anecdotal accounts indicated that tank battles had taken place during the 2003 Iraq War. He also met with representatives from Iraqi ministries, NGOs, doctors, and residents contaminated areas. His report is one of the first to exhaustively document the use of DU weapons in the Iraq by the US and UK, as well as clean-up and decontamination efforts carried out by the Coalition Provisional Authority (Zwijnenburg 2013). Independent academic scientists have detected elevated concentrations of uranium in soil samples from Mosul, suggesting that DU weapons have also been used in military offensives in the Ninawah governorate (Fathi, Matti et al. 2013).

In 2016, George Washington University publicly-released data on coordinates obtained from the US Airforce which they originally obtained via a Freedom of Information Act request (Oakford 2016). The data contain precise locations of 783 out of 1,116 airstrike carried out by DU-armed A-10 Warthogs in Iraq between March 20 – April 15, 2003. While the data do not contain total amounts of DU rounds fired during each strike, they do indicate a far more widespread use of DU during the 2003 Iraq War than had previously been indicated. The target locations are scattered across Iraq, in every governorate of Iraq (Oakford 2016). The data show where DU-armed flight sorties took place in 2003, indicating a significantly larger area was impacted by DU use than was previously reported, including in populated areas and cities.

During the first Gulf War, DU weapons were primarily used against heavily armored targets, often along highways or in remote desert areas where the tank battles took place. However, in 2003, the nature of warfare changed, and DU weapons were used (and continue to be used) against a far wider range of targets, including in urban warfare settings. The 2016 data released by George Washington University also confirms the use of DU weapons in populated areas (Oakford 2016). The use of DU in populated areas, against trucks, buildings, or human targets, is alarming, because it dramatically increases the risk of exposure faced by the Iraqi population (Zwijnenburg and Weir 2016). It also complicates clean-up, remediation, and decontamination of DU-impacted sites (Zwijnenburg and Weir 2016).

2.3.3 Clean up, storage, and scrap metal recycling of DU contaminated materials

Tracing the distribution of DU in Iraq is complicated by the lack of transparency regarding clean up, transportation, disposal, and recycling of DU contaminated materials in the country (Zwijnenburg, Weir et al. 2014). The lack of transparency speaks to the political-determinants of health, and the politization of DU contamination in Iraq. According to a 2003 report by UNEP, "most heavy military equipment" contaminated with DU (e.g. destroyed tanks and other heavily armored vehicles) had been relocated from battle zones to scrap metal disposal sites (UNEP 2003). However, no information has been published by the US, international organizations (IAEA, WHO, or UNEP), or the Iraqi government on the locations where clean-up has taken place, the methods for equipment removal and transportation, or the final storage locations for contaminated materials (Zwijnenburg 2013). One site suspected to have received some of the relocated tanks in vehicles is the Umm-Qasr scrap metal storage site (UNEP 2003).

Other reports, however, have provided evidence that DU-contaminated military equipment is still littered across Iraq, including in towns and populated areas (Zwijnenburg, Weir et al. 2014). Furthermore, there is evidence that scrap metal disposal sites have become unregulated sources for scrap metal recycling, and that military equipment is actively removed from those sites and transported to informal recycling facilities and sites, further dispersing DU throughout the country, including into Kurdish regions of northern Iraq, where informal metal recycling is widespread (Zwijnenburg, Weir et al. 2014).

2.4 Depleted uranium: Biokinetics and mechanism of toxicity

The above section provided a summary of the amount and distribution of weaponized uranium in Iraq. Although precise data is lacking, the information available provides a general idea of places and degree to which the Iraqi population has been exposed. What follows is a discussion of the biokinetics and mechanism of toxicity of depleted uranium; in other words, how exposure can translate into adverse patient-important health outcomes. Patient-important outcomes (PIOs) include measure of mortality, morbidity, disability, or functionality that affect patient health and perceived well-being (Yordanov, Dechartres et al. 2018). According to Sir Austin Bradford Hill's Criteria, plausibility is one of nine elements for establishing causality. This section describes the plausible pathways by which chronic exposure to weaponized uranium could cause biological damage.

Unlike many other environmental toxicants, uranium possesses both chemical and radiological toxicity (Bleise, Danesi et al. 2003, Armstrong, Brenner et al. 2012). So, this section will be divided into two subsections, addressing the mechanisms of

each toxicity. The first subsection (chemical toxicity) will discuss routes of exposure and absorption efficiencies for different uranium compounds by each route. It will also summarize the metabolism and distribution of uranium once it enters the blood stream, followed by biokinetics of storage and excretion. Finally, it will describe both the hypothesized mechanisms of chemical-induced toxicity at the cellular level and the evidence for observable effects at target sites. The second subsection (radiological toxicity) will address the fundamental concepts of radiation exposure and dose, as well as the zero-threshold hypothesis of radiation-induced health effects. It will conclude with a focused discussion on the processes by which internalized uranium can cause radiological damage at target sites.

2.4.1 Chemical toxicity

The variation in chemical toxicity of uranium comes three sources: characteristics of uranium compounds, aspects of exposure (route, dose, and duration), and individual susceptibility. Because depleted uranium is chemically identical to natural uranium, its chemically-induced toxicity is also the same, and while *in vitro* and *in vivo* studies on the chemical effects of depleted uranium are sparse, the volume of toxicological experimental research on natural uranium is large (HHS 2013). Therefore, the biokinetics and mechanism of toxicity of depleted uranium must be partly inferred from the evidence regarding natural uranium (HHS 2013).

2.4.1.1 Elemental speciation in warzones

When uranium metal (like the kind used in conventional uranium weapons) is exposed to air, it rapidly reacts with oxygen to form new uranium compounds

(elemental species), with varying solubilities and valence states (Handley-Sidhu, Keith-Roach et al. 2010). Although there is no rule-of-thumb for deducing toxicity from individual elemental species or their characteristics, understanding speciation of a toxicant is still integral to constructing the pathways through which exposure can lead to health risks (Apostoli, Cornelis et al. 2006).

To determine the speciation of uranium aerosols, the US Army launched a multi-phase experiment (named "The Capstone Study") in 2004 to determine the quantity and character of uranium compounds generated when depleted uranium munitions are fired on heavily armored vehicles, such as an Abrams tank and Bradley Fighting Vehicles (HHS 2013). An elaborate, enclosed facility was constructed for the study, designed to simulate realistic environmental conditions and complete with cutting-edge monitoring equipment (Parkhurst and Guilmette 2009). The study found that upon contact with a heavily armored target, 30-70% of a uranium penetrator becomes aerosolized, the majority of which forms U_3O_8 or UO_3 compounds, as well as a small amount of $UO_3 \cdot 2H_2O$ (Parkhurst and Guilmette 2009). The composition of uranium compounds in aerosol particles varied by particle size. The largest particles were composed primarily of U_4O_9, while the smallest particles contained the highest percentages of U_3O_8 or UO_3 (Parkhurst and Guilmette 2009). The force of impact, and thus the burning temperature of uranium, has also been found to affect the formation of compounds; the higher the temperature, the less soluble the oxides that are formed (Schott, Brand et al. 2006).

However, not all uranium munitions used in warzones strike hard targets, and thus the capstone study results do not completely represent the oxidation and environmental fate weaponized uranium (Handley-Sidhu, Keith-Roach et al. 2010). It is

estimated that aircraft-fired uranium munitions miss their target 90% of the time, and those that miss can become embedded in soil or sand, meters deep (Papastefanou 2002, Handley-Sidhu, Keith-Roach et al. 2010). The US military has also used uranium weapons in urban warfare contexts against buildings or other "soft targets" (Oakford 2016). Upon contact with soft targets, a significantly smaller portion of the uranium penetrator is aerosolized (<10%) (Handley-Sidhu, Keith-Roach et al. 2010).

Under most environmental conditions, uncombusted uranium metal fragments corrode to the insoluable compound uraninite (UO_2), but under acidic conditions, uranium metal (valence state 0) will react to form the soluble uranyl ion UO_2^{2+} (Handley-Sidhu, Keith-Roach et al. 2010). In the Balkans, it was estimated that time frame for complete corrosion of uranium penetrators buried in soil was 20 years (Handley-Sidhu, Keith-Roach et al. 2010).

2.4.1.2 Exposure

There are four routes by which individuals can be exposed to weaponized uranium: ingestion, inhalation, dermal contact, and embedded fragments. For natural uranium at background levels, ingestion is the primary route of exposure (i.e. through drinking water and diet), and the average daily dietary intake of uranium is between 0.9–1.5 μg (HHS 2013). Natural uranium is typically found at higher concentrations in soil than in air or water, with little tendency for bioaccumulation or biomagnification. Therefore, consumption of root crops (and thus soil residues which have adsorbed to the roots) is thought to be the greatest source of uranium exposure for the majority of people (HHS 2013). The amount of uranium adsorbed to root crops is determined by the uranium concentration in the soil, which can be elevated by the use of phosphate

fertilizers, proximity to uranium mines and processing facilities, and the testing or use of uranium weapons. In drinking water, uranium levels vary widely around the world, with an average concentration of 1.19 μg/L. For inhalation, the average daily intake of uranium at background levels (0.001–0.01 μg/day) is very small (HHS 2013). Because most uranium compounds found in soil are insoluble, the dermal route of exposure is considered insignificant for the general population. In places were weaponized uranium has been used, people may face exposure levels above background levels, particularly from inhalation of uranium aerosols or internalization from embedded weapons fragments.

In addition to route of exposure, dose and duration are important factors in determining health hazards and possible toxic effects of weaponized uranium (Giannardi and Dominici 2003). Dose refers to the amount of a substance that one is exposed to, and duration is the length of time over which one is exposed (HHS 2013). High dose, short duration is referred to as an acute exposure, while low dose, long duration is referred to as a chronic exposure. It is not within the scope of this thesis to calculate estimated doses of uranium compounds to which the Iraqi population has been exposed, but based on the exposure scenarios described previously, we can ascertain that there is likely widespread chronic exposure to weaponized uranium in US-conflict zones in the country, as well as cases of acute exposure (Giannardi and Dominici 2003).

2.4.1.3 Absorption

Solubility, and hence the ability of uranium to be absorbed into the bloodstream, varies between uranium species. Particle size and route of exposure also affect absorption rates. The primary mechanism by which uranium is absorbed is

diffusion, but in the lungs, large insoluable particles are also absorbed via phagocytosis (Tasat, Orona et al. 2012). According to the US Agency for Toxic Substances and Disease Registry (ATSDR), up to 5% of inhaled uranium will enter the bloodstream. Similar amounts (1-6%) of ingested uranium will be absorbed via the gastrointestinal tract, and a very small portion of uranium (<1%) will be absorbed in cases of dermal exposure (HHS 2013). These proportions are generalizations made from the available literature about absorption rates of different uranium species. However, it is reported that even across species of different solubilities, a fraction of the uranium internalized through any route will enter systemic circulation within days or hours of exposure (Prat, Bérenguer et al. 2010, HHS 2013).

2.4.1.4 Metabolism

The metabolism and biotransformation of uranium compounds *in vivo* is not well understood (Craft, Abu-Qare et al. 2004). What is known, is that once insoluable uranium compounds have been absorbed and entered plasma fluid, they are broken down, leading to the formation of uranyl ions which have a strong affinity to recomplex with enzymes, bicarbonates, citrate, and proteins (HHS 2013); a large portion forms ionic uranyl hydrogen carbonate complexes (Prat, Bérenguer et al. 2010). The primary phase I metabolic pathway by which uranium compounds are modified is oxidation, and an important antioxidant involved in phase II conjunction of uranyl ions is glutathione (GSH) (Tasat, Orona et al. 2012, Obeid, Oertel et al. 2016).

2.4.1.5 Distribution & Storage

A large number of pharmacodynamic models have been created to describe the typical distribution and storage patterns of uranium in the human body (HHS 2013). The most recent model published by the International Commission for Radiological Protection (ICRP) is ICRP69 (Bertelli, Lipsztein et al. 1997). **Figure 2** displays the complex systemic circulation of uranium, including its main retention sites, as presented by the ICRP69 model (Bertelli, Lipsztein et al. 1997).

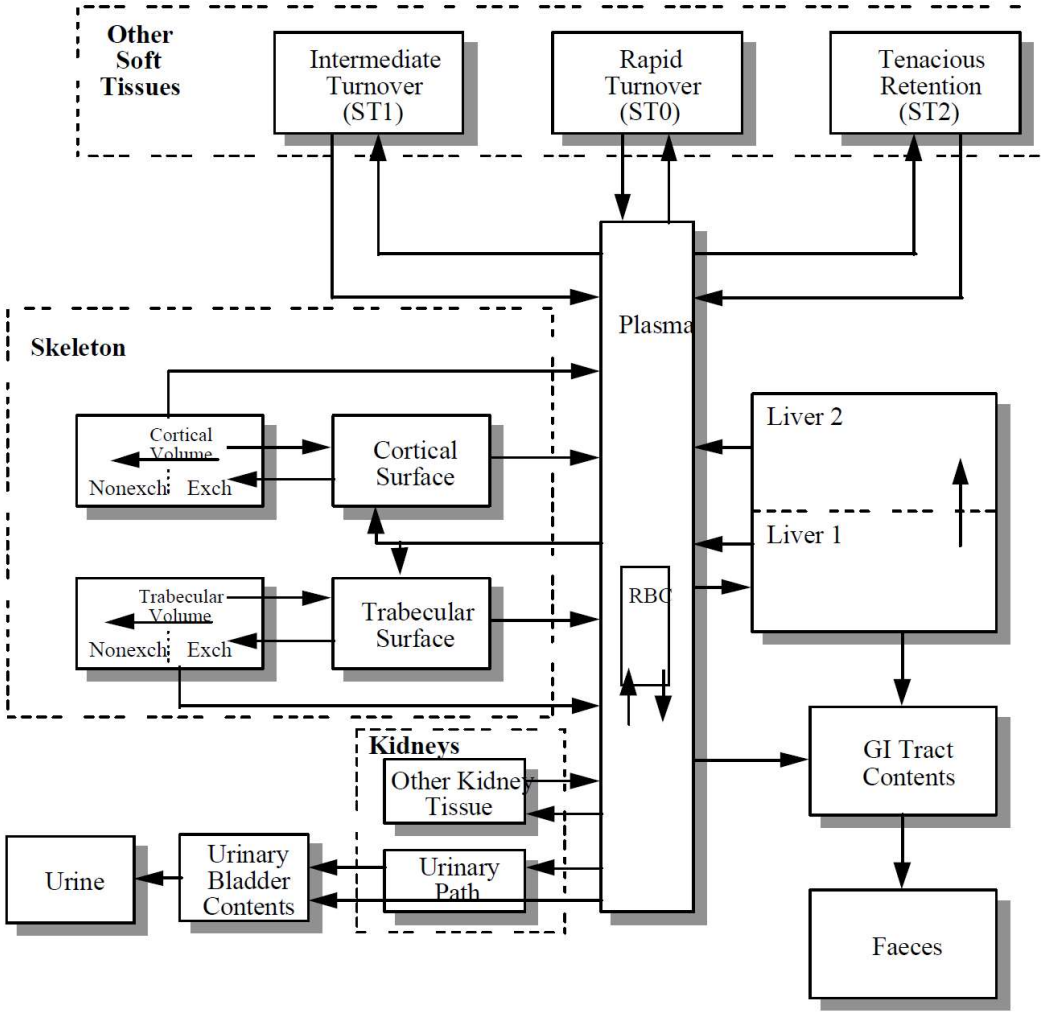

Figure 2. ICRP69 model of uranium systemic circulation

The typical adult human body contains 90 μg of uranium, two-thirds of which is stored in bone, followed by 16% in the liver, with the remaining portion stored in the kidneys (8%) and other tissues (10%) (HHS 2013). The primary concern for individuals exposed to weaponized uranium are insoluble uranium compounds, a large fraction of which are retained (long-term) in alveolar region of the lungs or pulmonary lymph nodes when absorbed via the respiratory tract (biological half-time of 4 years) (Katz 2014). In the lungs, uranium compounds will slowly solubilize and continue to enter the blood stream (Arfsten, Still et al. 2001). Of the total amount of uranium that enters the blood stream (by any route of exposure) as insoluble compounds, 85% is deposited in the bones where it also retained for long periods (biological half-time of up to 2.5 years) (Craft, Abu-Qare et al. 2004). On bone surfaces, uranyl ions are readily exchanged with calcium ions, but are then retained on bone surfaces for longer periods than calcium (Kurttio, Komulainen et al. 2005). The ability of uranium to cross the blood-brain barrier and placental barrier has been demonstrated in both animal experiments and human observational studies (Katz 2014).

2.4.1.6 Excretion

The primary routes for uranium excretion are urine and feaces. Two-thirds of the uranium that enters the blood (either through direct absorption or re-released through bone-turnover) is filtered in the kidneys and excreted in urine within 24 hours (HHS 2013). The normal range for uranium excretion levels in urine are between 0.04-0.5 μg/L (Faa, Gerosa et al. 2018). Of the uranium that is ingested, more than 95% is not absorbed and is excreted in the faeces (Tasat, Orona et al. 2012). Excretion of

uranium via hair is considered insignificant in terms of biologic toxicity, but is relevant to the biomonitoring of exposed populations.

2.4.1.7 Mechanism of action at target sites

- *Kidney*

The most frequently cited target of chemically-induced uranium toxicity is the kidney (HHS 2013). Evidence from animal studies reveals that uranium doses above background level damage kidney proximal tubular cells, and epidemiological studies on populations exposed to high uranium concentrations in drinking water have found associations with renal dysfunction, determined via measurements of urine levels of albumin, β2-microglobulin, glucose, and protein HC (HHS 2013). One proposed mechanism of uranium nephrotoxicity is the disruption of the electron transfer chain in renal mitochondria. In an experimental study of mice renal mitochondria, uranium ions were shown to interfere with the electron transfer chain, leading to the formation of reactive oxygen species as well as lipid peroxidation and glutathione oxidation, which ultimately caused damage to the mitochondrial outer membrane (Faa, Gerosa et al. 2018).

- *Bone*

The second major target of uranium toxicity is the bone marrow and bone surface matrix (Asic, Kurtovic-Kozaric et al. 2017). Two *in vitro* experiments on human osteoblast cells led by Alexandra Miller of the US Armed Forces Radiobiological Research Institute (AFRRI) have shown that exposure to depleted uranium caused chemically-induced neoplastic changes in the cells, altered tumor suppressor proteins, and caused a nearly 10-fold increase in cell division (Miller,

Blakely et al. 1998, C. Miller, Xu et al. 2002). *In vivo* animal experiments have also found that uranium complexes have a tendency to bind with the cell membranes of osteoblast cells, inhibiting bone formation, which suggests that uranium exposure may contribute to osteoporosis or other bone diseases (Tasat, Orona et al. 2012).

Because bone marrow (a major storage repository for uranium) is the site of white and red blood cell production, many epidemiological studies on population exposed to uranium have explored associations with myeloid malignancies and leukemia (Durakovic 2016). In Bosnia and Herzegovina (where depleted uranium munitions were used by NATO during the Yugoslav Wars 1992-1999), myeloid malignancies (including acute myeloid leukemia, chronic myeloid leukemia, and myelodysplastic syndrome) were more than three times more frequent among an exposed population in Hedzici than an unexposed control population in Ilijas (Besic, Muhovic et al. 2017). Two studies of Danish soldiers who were exposed to depleted uranium during the Balkan Wars and the 2003 Iraq War found that the veterans faced elevated risks of bone cancers compared to nondeployed soldiers (Katz 2014).

- *Lung*

Because the primary route of exposure to weaponized uranium is inhalation, the lungs are also an important target site for toxicity. Inhaled DU particles of <5 μm will reach the alveolar region of the lung (Hon, Österreicher et al. 2015), where insoluble compounds will have a pulmonary half-life of about 4 years (Briner 2010). In rat lungs, uranium (delivered via nasal inhalation) has been found to decrease the antioxidant potential of epithelial cells, reduce cell proliferation, and generate superoxide anions (Katz 2014). In human observational studies of uranium miners in the United States (carried out in the 1970's and 1980's), lung cancer has been

investigated as a possible adverse health outcome associated with uranium exposure (HHS 2013). These studies found excess rates of lung cancer among uranium mine workers, but conceded that the effects were more likely to have been caused by uranium's decay progeny (e.g. radon gas), than uranium itself (HHS 2013).

- *Brain*

Uranium has been shown to cross the blood brain barrier, and ingested uranium accumulates preferentially in the hippocampus, while inhaled uranium accumulates mostly in the olfactory bulb (Faa, Gerosa et al. 2018). Stress has been shown to reduce the effectivity of the blood brain barrier, leading to increased transfer of heavy metals and other contaminants (Barber, Hancock et al. 2007). Hence, populations residing in warzones, experiencing heightened psychological stress, are at a greater risk for experiencing neurological toxicity associated with uranium exposure (Tournier, Frelon et al. 2009).

Animal studies have shown that in rat brains, depleted uranium elevated superdioxide dismutase, catalyse, and glutathione peroxidase activities the cerebral cortex (Katz 2014). Following injected doses of 1 mg depleted uranium/ kilogram body weight, increases in brain lipid peroxidation in rats has also been observed (Katz 2014). Changes in brain lipid peroxidation in rats has been shown to be associated with behavioral changes, including decreased spatial memory (Briner 2010).

- *Sperm*

Reproductive cells (e.g. sperm) undergo high rates of cellular division, and thus are highly sensitive to xenobiotics. However, contradictory results exist among experimental animal studies that have investigated the impact of uranium on fertility and sperm count (HHS 2013). In one study of male mice fed 5.6 mg U/kg/day in

drinking water, decreased fertility was found among exposed mice. But in another study of male mice fed 14 mg U/kg/day by gavage, reduced sperm counts and fertility was not observed (HHS 2013).

- *Fetus*

In their 2013 update of the toxicity profile for uranium, the ATSDR reported, *"We do not know whether uranium can harm an unborn child. No scientifically strong human study that has shown birth defects due to uranium exposure has been identified"* (HHS 2013). This statement contradicts a large body of evidence (from both animal experiments and human observational studies) which has documented the teratogenic effects of uranium exposure (Hindin, Brugge et al. 2005). There are a few mechanisms by which uranium can affect fetal development. First, uranium is capable of crossing the placental barrier, leading to direct exposure to the developing fetus; approximately 10% of uranium content in maternal blood is transferred to the fetus (Alaani 2011). Like other heavy metals, uranium can cause oxidative stress in womb, disrupting embryonic development (Esteban-Vasallo, Aragonés et al. 2012). Absorbed uranium can also induce chromosomal aberrations, and DNA strandbreaks (to be discussed further in the next section on radiologic toxicity). If such mechanisms occur in reproductive cells (maternal or paternal), or in embryonic cells, they can culminate in birth deformities (Foster, Evans et al. 2017). Finally, heavy metal exposure can reduce maternal uptake of folic acid, leading to folate deficiency, which in turn is associated with congenital birth defects (Al-Sabbak 2012).

2.4.2 Radiologic toxicity

According to the retired US Army Medic, Dr. Asaf Durakovic, the term depleted uranium "is a semantic attempt to reduce awareness of the significance of its hazard to the biosphere" (Faa 2018).

A commonly repeated refrain (including by the ATSDR) is that toxicity of depleted uranium is due to its chemical, not radiologic, properties. However, many studies have indicated otherwise (Hindin, Brugge et al. 2005, Miller and McClain 2007, Briner 2010, Katz 2014, Faa, Gerosa et al. 2018). While the ATSDR toxicity profile for uranium (updated in 2013) claimed that uranium was not classified as a carcinogen (HHS 2013), the 2012 monograph on radiation by the International Agency for Research on Cancer (IARC) classified all isotopes of internalized uranium as a Group 1 carcinogens *due to their alpha-emitting (radioactive) properties* (Armstrong, Brenner et al. 2012). This section will begin will a brief introduction to radiation and measurements of radiation exposure, and then discuss specific mechanisms by which uranium alpha-emission can induce genetic damage.

The potential for nuclear radiation to cause biological damage stems from its ability to deposit energy on atoms or molecules, causing them to release or absorb electrons and become ionized (Goodhead 1994). Hence nuclear radiation, unlike other forms of electromagnetic radiation such as radio-waves or microwaves, is referred to as ionizing radiation. Ionized macromolecules in cells can cause single- and double- strand DNA breaks, as can free radicals generated by the ionization of water molecules inside of cells (Goodhead 1994).

Biological damage from nuclear radiation can only occur if exposure has taken place. In toxicology, the term "exposure" has two meanings. In reference to ionizing

radiation, the term *exposure* denotes "denotes physical interaction of the radiation emitted from the radioactive material with cells and tissues of the human body" (HHS 2013). This definition of exposure in the *radiological sense* differs from definition of exposure in the *chemical sense*, e.g. the phrase "route of exposure" used in reference to chemical toxicants. Chemical toxicants usually only cause biological damage once they are absorbed (i.e. internalized), and their "route of exposure" (inhalation, ingestion, or dermal contact) determines the mechanism and efficiency by which they are or aren't absorbed into the bloodstream. Because radiation involves the projection of particles and energy waves through space, it can cause internal biological damage even if no radionuclide has been absorbed into the bloodstream. However, the differences in penetrating power between types of radiation (alpha, beta, and gamma) make the differentiation between exposure to radiation emitted from radionuclides external to the body (i.e. external radiation exposure) and radiation emitted from radionuclides that have been absorbed into the bloodstream (i.e. internal radiation exposure) essential.

The SI unit for measuring *external* radiation exposure is coulomb/kg of air (C/kg), but the most widely used conventional unit is the Roentgen (R), named after Wilhelm Roentgen whose discovery of x-rays prompted the later discovery of radiation emitted from uranium salts. Both units of measurement apply only to gamma radiation, because gamma radiation is the only environmentally-relevant type of radiation capable of traveling meaningful distances through air or penetrating the skin (USGS N.D.). Uranium, and most of its decay progeny, only weakly emit gamma radiation, therefore exposure (in the radiological sense) is typically not measured for uranium (USGS N.D.). Instead, with regard to the radiotoxic properties of uranium, environmental radiobiologists are more concerned about dose.

There are three types of radiation dose measurements that are commonly assessed: absorbed dose, equivalent dose, and effective dose (CNSC 2014). Absorbed dose is defined as the amount of energy transferred from a radiation particle (alpha and beta radiation) or electromagnetic wave (gamma radiation) to the material through which it passes. In other words, it describes the amount of energy absorbed by a tissue or organ. The SI unit for absorbed dose is the Gray (Gy) and is equal to one joule of energy deposited per kilogram of mass (J/kg) (CNSC 2014). Equal absorbed doses, however, do not always produce equal biological effects, so the equivalent dose was invented as a measure of biological impact caused by absorption of radiation, and it is specifically intended for radiation protection purposes (CNSC 2014). The SI unit for equivalent dose is the Sievert (Sv) and, like the Gray (Gy), is also equal to one joule of energy deposited per kilogram of mass (J/kg) (Adlienė and Adlytė 2017). In calculating the equivalent dose, the absorbed dose to a particular organ or mass of tissue is multiplied by weighting factors for each type of radiation (alpha, beta, or gamma) (Adlienė and Adlytė 2017). Finally, the effective dose accounts for the differences in radiosensitivity between different tissues and organs, by multiplying the absorbed dose by weighting factors for both type of radiation and type of tissue. The SI unit for effective dose is also the Sievert (Sv) (Adlienė and Adlytė 2017).

The accepted model for adverse health impacts (including cancer) for ionizing radiation is a linear-no-threshold model. Meaning, any amount of exposure to ionizing radiation increases the risk of adverse health effects, although at low doses, the risks may be too small to detect in a population. The maximum allowable uranium air concentration set by the US Nuclear Regulatory Commission is 45 μg/m3 for soluble uranium compounds and 200 μg/m3 for insoluble uranium compounds (Giannardi and

Dominici 2003). According to radiation measurements carried out by Iraqi scientists in the mid-90's, residents of Basrah City, were estimated to receive a full-body, external annual radiation dose of 442 – 577 mSv (Al-Azzawi 2006). However, these findings have been disputed (Fahey 2004). A health risk assessment carried out by independent Italian scientists in 2003, estimated that exposure via inhalation was unlikely to exceed 1 μSv/year for the residents of Basrah, unless the air concentration of uranium was high (>1700 μSv) (Giannardi and Dominici 2003).

Because uranium in an alpha-emitter, radiologically-induced toxicity can only occur when internalized (Durakovic 2016). Once internalized, uranyl ions have a strong affinity to bind with DNA (Alaani, Tafash et al. 2011). Depleted uranium has a specific activity of 14.9 Bq/mg (Giannardi and Dominici 2003). This means that a person with 90 ug of internalized uranium (the world average) will experience 1 alpha-particle emission approximately every 10 seconds. Each alpha-particle emitted from uranium possesses an energy level of 4.2 million electron volts, whereas a DNA strand can be broken with only 10 electron volts of energy (Abdul-Wahid 2009). In a multi-generational mouse study, Alexandra Miller and colleagues from the Armed Services Radiobiological Research Institute showed that as paternal DU-dose increased, the higher the frequency of genetic mutations of progeny (Miller, Stewart et al. 2009). Within the epidemiological literature, the incidence of chromosomal aberrations in the Bosnia-Herzegovina population has been examined. Ibrulj et al (2007) found the frequency of dicentric chromosomes was higher among a sample of participants from Hadzici (occupationally exposed to DU in a tank repair facility), than among participants from Sarajevo and Posusje (control groups) (Ibrulj, Haverić et al. 2007). In a study of British veterans who had served in the first Gulf War in Iraq, or the Balkan

Wars, Schroeder et al (2003) found that the frequency of dicentric chromosomes were five times higher among DU-exposed veterans than among a control group in Germany (Schroeder, Heimers et al. 2003).

2.5 Debate over impact of DU on public health in Iraq

2.5.1 A timeline of evidence and arguments

Even before the first Gulf War began, the US army anticipated that the health impacts of DU in Iraq could trigger public backlash and debate (Diehl, Fahey et al. 1999). A report published by the US Army in July 1990 (one month before Iraq invaded Kuwait) stated: "Following combat, the condition of the battlefield, and the long-term health risks to natives and combat veterans may become issues in the acceptability of the continued use of DU kinetic energy penetrators for military applications" (Diehl, Fahey et al. 1999).

In January of 1992, the first cohort of Gulf War veterans were diagnosed with unknown illnesses collectively referred to as "the Gulf War Syndrome" (GWS) and exposure to DU was posited as a possible cause (Lang 2001). Between 1992-1998, at least seven studies were carried out to investigate causes of GWS, including three by the US Department of Defense. The studies found no excessive hospitalizations, no increase in birth defects, no elevated mortality rates, and no association between illness and environmental exposures (including DU) among Gulf War veterans (Lang 2001).

At the same time that the US Department of Defense was investigating DU health risks among Gulf War veterans, Iraqi doctors and independent researchers were beginning to raise the alarm about the possible health risks faced by the Iraqi population (Fahey 2004). In 1993, a member of the Harvard medical team investigating post-war

health in Iraq and Kuwait, Dr. Eric Hoskins, wrote an op-ed in the New York Times decrying the high prevalence of birth defects that he had observed during a trip to Basrah, and speculating that DU may be the cause (Mathews 1993). Meanwhile, a network of activists in the US published a landmark report "Uranium Battlefields Home & Abroad: Depleted Uranium Use by the U.S. Department of Defense", which collected evidence indicating that DU was more harmful than the US government had publicly claimed (Fahey 2004). Also in 1993, scientists from the Iraqi Atomic Commission and Baghdad University began conducting radiometric investigations around battle sites in Southern Iraq (Al-Azzawi 2006). In 1997, the first conference on DU was organized in the US by an NGO called Military Toxics Project (MTP) (Fahey 2004), and in 1998, the government of Iraq submitted a report to the Office of the United Nations Commissioner for Human Rights claiming the DU weapons were responsible for a raise in cancers and birth defects in the country (Salman 2008).

Throughout the 1990's, the US government continued to deny that any adverse health impacts (among veterans or Iraqi civilians) were attributable to DU, but the debate remained low-profile and did not garner significant media attention (Fahey 2004). It wasn't until after the Balkan wars (1991-1999) that the DU debate took off, and took on new political and ideological dimensions. Although the US initially denied deploying DU weapons in the Balkans, in March of 2000, the Secretary General of NATO admitted for the first time that the US used DU rounds in Kosovo (Lang 2001). According to the DU scholar Dan Fahey, this event marked a turning point in the DU debate and "the decline of rational discourse about DU" (Fahey 2004). In the following months 12 British soldiers that served in the Balkans announced that they would sue NATO over health impacts due to DU exposure, the governments of Portugal and Italy

accused NATO of a cover-up, the European parliament passed a resolution calling on NATO members to implement a moratorium on DU weapons (Lang 2001), and the WHO issued a call for "flash funds" to study the impact of DU on public health in Iraq (a study that was never realized) (WHO 2001). Slobodan Milosevic (Serbia), Saddam Hussein (Iraq), and Yasser Arafat (Palestine) each made public statements proclaiming that DU was responsible for public health catastrophes in their respective countries (Fahey 2004).

The new political attention paid to DU weapons in the early 2000's was mirrored in western media sources, which began making exaggerated and unfounded claims about the impact of DU on public health in Iraq (Fahey 2004). Some articles equated the use of DU weapons with an act of genocide (Zwijnenburg 2013). In the lead up to the 2003 Iraq War, rhetoric and propaganda became irrevocably infused into the public discourse over DU weapons, as both the governments of Saddam Hussein and George W. Bush manipulated perceptions of DU to boost their own political agendas (Fahey 2004).

Within the academic literature, there was a more tempered approach to the DU debate; expert reviews unanimously argued that a lack of human observational studies and epidemiological evidence prevented firm conclusions from being drawn about the public health impacts of DU in Iraq (Huggan 2007, Levy and Sidel 2013).

2.5.2 Controversy, cover-up, and publication bias

In the midst of the media and academic discourses over DU, a number of controversial incidents occurred which suggest that interference, specifically from the US government, has affected the production on research into DU toxicity.

The first controversy concerns Asaf Durakovic M.D., a Croatian radiobiologist who became a US Army Medical Corps colonel and served in the 1991 Gulf War (Lang 2001). As chief of the Nuclear Sciences Division at the Armed Forces Radiobiology Research Institute, Dr. Durakovic was the first physician to recognize symptoms of radiation exposure among Gulf War veterans. When he sent urine samples from his patients for uranium analysis, the samples and their accompanying paperwork were lost. After receiving a warning from his superiors within AFRRI to discontinue that line of research, Durakovic was terminated from his position in 1996 (Lang 2001).

Before that, in 1992, Dr. Siegwart-Horst Gunther (a German epidemiologist and president of Yellow Cross International) visited Basrah to investigate the impact of the first Gulf War on child health in Iraq (Norton-Taylor 1999). During his visit, children showed him spent shells that they had collected, and Dr. Gunther decided to bring one back to Germany for radiologic analysis. The day that he went to deliver the spent shell to a lab in Berlin, he was arrested under the pretense of importing "dangerous radioactive material". Although the charges were eventually dropped, his investigations into the health impacts of DU were halted (Wagner 2005).

In 1998, Dan Fahey, an independent DU researcher, uncovered data on friendly-fire incidents with DU munitions during the first Gulf War through a Freedom of Information Act request, which contradicted the US Army's official statistics on the number of US veterans with embedded DU fragments (Fahey 2004). Before filing the request, he claims that a Pentagon intelligence officer had threatened him with a lawsuit, and sought to discredit him among veterans groups in the US (Fahey 2004).

In 2001, Dr. Keith Baverstock, a senior radiation adviser at the WHO, completed a study into DU toxicity, but according the Dr. Baverstock, the WHO

prohibited him and his colleagues from publishing the results (Edwards 2004). According to Baverstock, the study found that civilians in Iraq faced unique exposure scenarios (due to the dry climate of Iraq, and re-suspense of uranium oxide dusts), which could lead heightened toxicity relative to veterans or populations in the Balkans (Edwards 2004). After retiring from the WHO in 2003, Baverstock told the Sunday Herald that he suspects the WHO suppressed the study at the behest of the IAEA. Concern about the IAEA's influence over the WHO's radiation health research dates back to 1959, when the two organizations formalized an agreement allowing the IAEA to oversee and give final approval over WHO radiation-related research (Hindin, Brugge et al. 2005).

Most recently, the WHO was implicated in a controversy related to a national birth defects study in Iraq. In 2011, the WHO partnered with the Iraqi Ministry of Health (IMOH) to conduct a household survey in 18 districts (from 8 governorates) in Iraq; 600 households from each district were surveyed, for a total of 10,800 households (IMOH 2013). The survey itself consisted of three questionnaires: one for the head of household, one for all ever-married women within the household, and one for following-up on reported cases of infants born with CBD. The questionnaires asked individuals to report the history of live-births, still-births, and births with CBD in the household between 1988-2012, for a 24 year assessment period. In total, >40,000 births were reported during that time period from households surveyed (IMOH 2013).

To date, a full report of the study's findings has not been published, nor has the complete data-set been made available for analysis by researchers outside of the IMOH or WHO. In September of 2013, the IMOH released a summary report of their results. The summary included two tables depicting results: one showing varying rates of CBD

(for all districts) overtime, and one showing varying rates of CBD (for the entire time-period) between districts. They found that from 2008-2012 an average of 23.7 CBD were reported for every 1000 births (CBD/1KB) across all districts surveyed, with mean rates ranging from 9.1 CBD/1KB in the Jimjamal district of the Sulaimaniyah governorate, to 39.7 in the Al Qaim district of the Anbar governorate. As the summary points out, the Iraq national mean is within the range of CBD rates reported for high-income countries like the United States (30CBD/1KB). The summary also concluded that no significant increase in CBD had occurred between 1988-2012. For the time period 1998-2008, the reported rates of CBD were virtually the same as the period 2008-2012. For the time periods from 1992-1997, and from 1988-1992, reported rates were lower than the more recent periods. However, the report attributes the lower rate to "memory-bias," rather than to a true difference. In conclusion, "the study provides no clear evidence to suggest an unusually high rate of congenital birth defects in Iraq," (IMOH 2013).

After the summary publication was released, the IMOH/WHO survey came under harsh and widespread criticism, from the public, the media, and the academic literature (Savabieasfahani 2013). "How the World Health Organization covered up Iraq's nuclear nightmare," was the title of one media critique, published by the Guardian online newspaper on October 13th, 2013, by investigative journalist and international security scholar Nafeez Ahmed (Ahmed 2013). The article begins by referring back to statements made by IMOH officials in an interview with the BBC earlier that year about the "damning evidence" of higher CBD rates in zones that came under heavy fire from US and coalition forces. It also references reports by medical doctors, and publications in peer-reviewed journals, which found "a high level of birth defects" throughout the

country in recent years, and in the district of Fallujah, a rate "13 times the rate found in Europe," findings which starkly contradict those of the IMOH survey. Why the contradiction? Ahmed finds blames the "politicizaion" of scientific research by WHO officials and the US government, which he claims have delegitimized the validity of the study and its "anonymous authorship" (Ahmed 2013).

Hons Von Sponeck, former UN Secretary General and Humanitarian Coordinator for Iraq, said "the brevity of this report is unacceptable," and Keith Baverstock, retired WHO radiation expert, said "it wouldn't pass peer-review in one of the worst journals," (Ahmed 2013). It is unclear what role the WHO played in the production of the report, and that organization has a conflict of interest in conducting a study which could provide criminalizing evidence against its primary financial donor, the US government. An interview with Dr. Keith Baverstock conducted by Ahmed, suggests that "there was reason to believe the research findings were compromised under political pressure." Baverstock claims that after his contributions concerning the genotoxicity of DU to a separate WHO project (which cleared "the US and UK of responsibility for environmental health hazards involved in DU deployment") were rejected, his own attempt to publish a DU-related study in a peer-reviewed journal was blocked by the WHO "because they didn't like its conclusions," (Ahmed 2013). Hans Von Sponek was also quoted in Ahmed's article as stating, "It seems that someone, somewhere clumsily decided that they would not release these damning findings [referred by IMOH officials], but instead obscure them," (Ahmed 2013).

The Lancet medical journal also published a critique raising questions about the validity IMOH study (Webster 2013). Rather than focusing on the potential "politicization" of the study, the Lancet critique focused on the potential flaws in the

peer-review process that the IMOH project underwent. It must be noted that these two sources of scientific error are interrelated, because a rigorous peer-review process is a key tool for identifying and correcting data manipulation and bias. Jaffar Hussien, WHO's Head of Mission in Iraq, told the Lancet that the IMOH project and report underwent extensive peer review by a team of international experts (Webster 2013). Despite Hussein's claim, the Lancet article posits that WHO's objective of meeting scientific standard in their peer-review process "may not have been fully achieved". Among the international experts who participated in the what the WHO calls a "peer-review process" was Simon Cousens, a professor of epidemiology and statistics at the London School of Hygiene and Tropical Medicine (Webster 2013). According to Cousens, the WHO "peer-review process" consisted of a single meeting, about 1.5 hours long, attended only by WHO-selected invitees. "I wouldn't classify that as thorough peer-review," Cousens told the Lancet. Other reviewers also reportedly raised concerns about the survey's methodology and geographic scope, concerns which were unaddressed (Webster 2013).

2.6 Systematic review: A tool to analyze and synthesize the evidence

This chapter has summarized the last 30 years of research and debate over the possible health impacts caused by the used of weaponized uranium in Iraq. Many recent review articles have been published which attempt to summarize the evidence regarding toxicity of weaponized uranium (Briner 2010, Hon, Österreicher et al. 2015, Asic, Kurtovic-Kozaric et al. 2017, Foster, Evans et al. 2017, Besic, Muhovic et al. 2018, Faa, Gerosa et al. 2018). However, only one review (on US Gulf War veterans) has adopted a systematic approach to surveying and synthesizing the literature (Gronseth

2005). One expert narrative review endorsed by the WHO and IMOH failed to include four relevant studies on the topic (Al-Hadithi, Al-Diwan et al. 2012), while an earlier review by the RAND corporation missed 62 relevant studies (Fahey 2004). This speaks to the need for a systematic review on the topic.

Systematic reviews have long been considered the highest tier of evidence in the field of clinical medicine and are increasingly considered so in the field of environmental health (Woodruff and Sutton 2014). Although never yet applied to the ecology of war, their thorough, transparent, and reproducible methods make systematic reviews the ideal tool for approaching controversial and politicized questions of environmental exposures.

The goal of applying a systematic review on this topic is to identify all human observational studies that have assessed associations between exposure to weaponized uranium and adverse patient-important health outcomes among the Iraqi population. Many sources have pointed out that, compared to Gulf War veterans, health impacts among civilian populations exposed to weaponized uranium have received scant attention (Faa 2018, Fahey 2004, The Lancet Oncology 2001). In the case of Iraq, where more DU has been used in combat than any other country, investigating the possible health effects caused by DU has been a priority for local scientists since the mid-90's. However, due to limitations imposed by the sanctions, much of that research has been inaccessible and was not debated in the international peer-reviewed literature. Hence, a systematic review, with a highly sensitive search strategy, has the potential to uncover that research, and bring it to light.

Adopting the Navigation Guide's systematic review methodology for human observational studies (Johnson, Sutton et al. 2014), this thesis also aims to synthesize and critically appraise all of the studies that it captures.

CHAPTER III

METHODOLOGY

3.1 Systematic review team

The first step in conducting a systematic review (SR) is to assemble a review team with relevant and diverse expertise (Woodruff and Sutton 2014). At a minimum, an SR team should include an individual with expertise in SR methodology, a medical librarian with expertise in developing search strategies for SRs, and researchers with adequate training to carry-out study selection and data abstraction (CDC 2017). Whether or not a review team should include a content expert (an individual with a strong background in and expert knowledge of the study question) is currently a topic of debate within the literature concerning SR methodology and development (Gøtzsche and Ioannidis 2012, Frampton, Livoreil et al. 2017). For SRs conducted under the umbrella of the Cochrane Collaboration, content area experts are required members of the review team, because of their ability to direct question formation and contribute to identification of unpublished studies (Higgins and Green 2011). However, it has been argued that content experts might also introduce bias into SRs, because of their *a priori* assumptions that might be at odds with the evidence (Gøtzsche and Ioannidis 2012). A practical solution to resolving the possible impartiality introduced by content experts, while maintaining their involvement and input, is to build a review team with diverse expertise (Frampton, Livoreil et al. 2017). Adopting this approach, our review team included members with expertise in systematic review methodology (Elie Akl, Lara Kahale), library sciences (Aida Farha), public health (Rima R. Habib, Omar Dewachi,

Mais Al-Lobaidy), environmental health (Rima R. Habib, Shelby Surdyk), medicine (Elie Akl, Omar Dewachi), and ecosystem management (Moustapha Itani).

3.2 Specification of the study question

The objective of this SR is to answer the following research question: Is environmental exposure to weaponized uranium associated with adverse health outcomes in the Iraqi population?

3.3 Eligibility criteria and PECOS statement

In order to answer the research question, we developed a PECOS (Population, Exposure, Comparator, Outcome, Study Design) statement. In evidence-based medicine (EBM), one of the most important tools for structuring an SR is the development of a PICO (Participants, Intervention, Control, Outcome) statement (Higgins and Green 2011). Randomized clinical control trials (RCTs) are considered the 'gold standard' in EBM, and thus the PICO statement is most suited for use in selecting reports of pharmaceutical RCTs which meet prespecified criteria regarding participant characteristics, intervention type (i.e. medication and dose), control type (i.e. placebo, alternative medication, or alternative dose), and outcome measured. In the discipline of environmental health, however, observational studies (not RCTs) dominate the literature. In fact, it has been argued that observational studies constitute the 'gold standard' in the domains of environmental health and toxicology (Woodruff and Sutton 2014). Therefore, environmental health researchers have adapted the PICO guidelines to the context of environmental exposures and non-experimental studies, leading to the development of the PECOS statement (Population, Exposure, Comparator, Outcome, Study Design) (Woodruff and Sutton 2014). The PECOS statement for this SR is

summarized in **Table 4.**

3.3.1 Population

The population of interest in this review consists of individuals (of any age) residing in Iraq at any time between 1990-2018, or children born to those individuals. Therefore, this review aims to capture studies whose participants include or are made up entirely of such individuals, excluding military veterans (of US or other nationalities) who fought during the 1990 or 2003 Iraq Wars. Our study aimed to focus exclusively on the Iraqi population due to their unique exposure scenario (chronic), which justified the exclusion of veterans who experienced short-term (acute) exposure. Furthermore, an SR on the health impacts of DU among US Gulf War veterans has previously been conducted, while no such review has been conducted for the Iraqi population (Gronseth 2005). Our decision to focus exclusively on the Iraqi population, as opposed to including studies on DU-exposed residents in the Balkans, is based on the differences in the environmental conditions between Iraq and the Balkans. Humidity, temperature, and soil acidity all effect the corrosion and environmental fate of uranium, meaning that the Iraqi and Balkans populations are likely exposed to different uranium oxide compounds, although the DU weapons used in armed conflicts in the two regions were the same (Handley-Sidhu, Keith-Roach et al. 2010).

3.3.2 Exposure

The exposure of interest in this review is metallic uranium that has been introduced to the environment in Iraq via the use of conventional weapons (i.e. non-nuclear missiles, bullets, and armor). Exposure to weaponized uranium will also include

its decay and corrosion products. These include the radioactive decay daughters of uranium, emitted radioactive energy and particles, and environmental compounds formed by uranium or its decay daughters. Studies will not be excluded on the basis of route, dose, or duration of exposure. Measures of exposure can include:

- Determination of the chemical content of environmental media such as soil, water, air, or plant and animal tissues;
- Assessment of radioactivity levels in environmental samples or sampling locations;
- Visual identification of uranium weapons, such as abandoned tanks or missile shells;
- Documentation of sites where uranium weapons were known to have been used, such as the site of a tank battle;
- Measurement of uranium content in human biological tissues, such as urine, blood, hair, or bone;
- Self-reported exposure to weaponized uranium;
- Residence at any location in Iraq since the first date the uranium weapons are known to have been used (1991).

3.3.3 Comparator

The comparator or control population of interest in this review consists of any individuals not exposed to weaponized uranium, or individuals exposed to lower levels. Comparators can include:

- Individuals living in areas of Iraq where uranium has not been detected, or where uranium weapons are not known to have been used;

- Individuals who had lower levels of uranium detected in their biological samples, or no uranium detected at all;
- Individuals residing in Iraq prior to the first use of uranium weapons (historical control);
- Individuals living outside of Iraq, in places where uranium weapons are not known to have been used.

3.3.4 Outcome

Regarding outcomes, this review aims to capture studies that measure or investigate patient-important health outcome in Iraq. Patient-important outcomes include mortality, morbidity, disability, or quality of life outcomes (Yordanov, Dechartres et al. 2018). For example, eligible studies may measure the association between uranium exposure and changes in the prevalence, incidence, geographic distribution, demographics (age, gender, etc.) of types of cancer or congenital birth defects (CBD) in Iraq. Studies were excluded which only assessed uranium exposure but did not measure or investigate an association between that exposure and a health or disease outcome. By this exclusion criteria, studies which detected of uranium in human biological samples (e.g. blood, urine, tissues, etc.), but did not also report health and disease outcomes among participants, were excluded. Studies which estimated a future health risk to the target population based on radiation doses calculated from measured environmental radiation levels were also excluded. While such studies are certainly relevant to assessment of health risks of uranium, they do not directly apply to the specific research question, and thus are not appropriate to include in the final data synthesis of this SR.

Finally, with regard to study design, our review aims to capture human observational studies, not experimental studies or clinical control trials. Included studies can have case-control, cohort, cross-sectional, or ecological study designs. We will exclude epidemiological reviews which do not contain or report primary research. We will also exclude experimental studies on either humans (clinical control trials) or animals, as well as *in vitro* studies of uranium toxicity.

Table 4. Detailed PECOS study eligibility criteria

Inclusion Criteria	Exclusion Criteria
Population	
- **Humans (of any age) residing in Iraq at any time between 1990-2018** - **Children born to those individuals**	- Non-humans - Military veterans (U.S. or other nationalities)
Exposure	
- **Chemical exposure to metallic uranium that has been introduced to the environment in Iraq via the use of conventional weapons (i.e. non-nuclear missiles, bullets, and armor)** - **Chemical exposure to decay and corrosion products of weapon uranium in Iraq** - **Physical exposure to ionizing radiation emitted from radioisotopes in weaponized uranium or its decay or erosion products**	- Physical exposure to UV radiation (e.g. solar radiation) - Physical exposure to ionizing radiation emitted from medical radioisotopes - Physical or chemical exposure to nuclear materials not originating from metallic uranium weapons used by US and coalition forces
Comparator	
- **Individuals not exposed to uranium** - **Individuals exposed to lower levels** - **Can include historical controls**	- Studies that document health impacts among an exposed population without comparison to a non-exposed (or lesser exposed) group or population
Outcomes	
- **Human health-relevant outcomes, including measures of general wellbeing, mental health, or self-rated health**	- Studies that measure the concentration of uranium (or decay/corrosion products) in environmental or human biological samples without measuring a health outcome - Studies that measure radiation levels in food, water, or environmental samples without measuring a health outcome
Study Design	
- **Observational study designs including case-control, case-report, cohort, and cross-sectional**	- Randomized control trials or other experimental study designs - Reviews (including systematic reviews) which do not include or report primary research

3.4 Search strategy

In order to ensure that SRs are transparent and reproducible, explicit details of the search strategy must be reported (Liberati, Altman et al. 2009).

A search strategy is made up of the methods by which SR authors assemble references of possible relevance, in order to later screen them for eligibility. While the PECOS statement and eligibility criteria act as a guide in creating a search strategy, a search strategy may be much broader or narrower than those criteria. Broadness or narrowness in an SR search strategy is referred to as sensitivity or specificity, respectively. The nature of the research question, the volume of literature on the subject, as well as logistical limitations such as number of SR team members and time constraints all effect the degree of sensitivity and specificity adopted by the SR team in the determination of their search strategy. A highly sensitive (broad) search strategy could return tens of thousands of references to be screened, including a large fraction of irrelevant ones which require a large amount of time and effort to assess for eligibility. On the flip-side, a very specific (narrow) search strategy may return only a few hundred results, which only require a small effort to screen, but which may fail to capture one or more highly relevant studies.

Construction of a search strategy begins with the identification of *concepts*, often drawn directly from the PECOS statement. A concept is a single theme or feature upon which you would like to gather relevant literature. In an SR search strategy, separate concepts are related through the use of the Boolean operator “AND”, as illustrated in **Figure 3**.

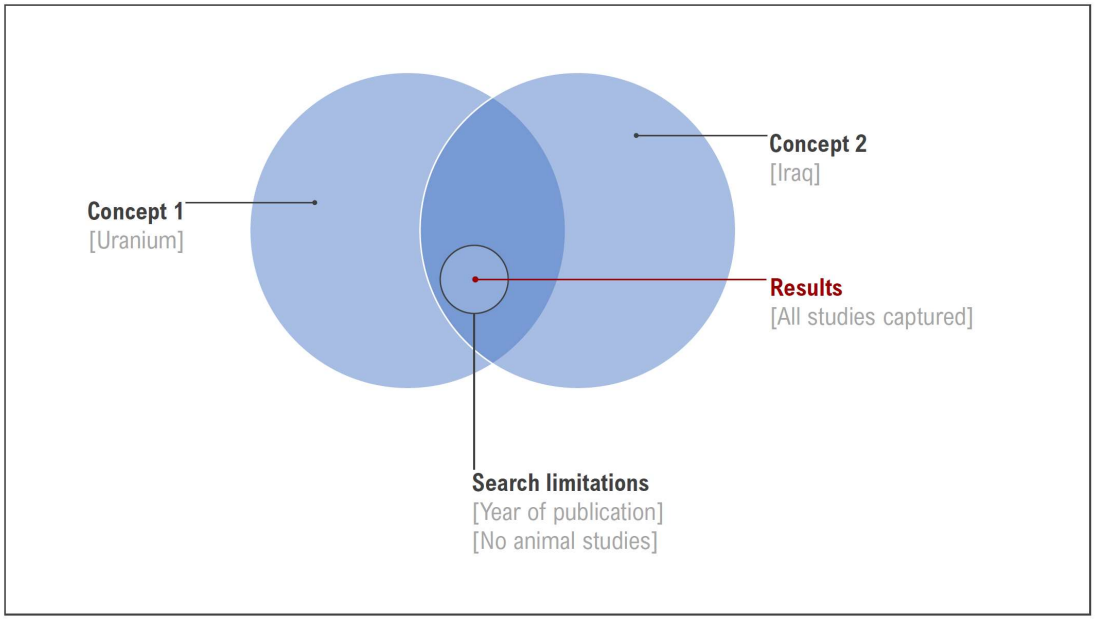

Figure 3. Venn Diagram illustration of the search strategy for this SR

3.4.1 Concept 1: Uranium

In this review, a key concept was metallic weaponized uranium. Initially, the authors of this SR believed that the term "depleted uranium" adequately described that concept for the purposes of the SR. To develop the concept, a comprehensive review of the literature, as well as consultation with content experts, was carried out to identify terms related to, or synonyms for, depleted uranium. We sought to develop a highly sensitive search strategy, gathering as many terms, synonyms, or abbreviations as possible. In this process, we discovered that uranium metal used in weapons and armor by US and coalition forces in Iraq during the first Gulf War and 2003 invasion may not have been limited to uranium that was depleted of U-235 isotopes (Alaani, Tafash et al. 2011). Therefore, we expanded this concept to include uranium metal of any isotopic ratio. Reviewing the literature further informed us that when uranium metal is introduced to the environment, it corrodes, forming by-products such as uranyl ions and

uranium-oxide molecules. These corrosion products were incorporated into the concept, because the introduction of weaponized uranium metal into the environment will lead to their presence in environmental media, and they may also impact the health of an exposed population. Names of the decay daughters of uranium, as well as the vocabulary for ionizing radiation, were also added to the concept.

3.4.2 Concept 2: Iraq

The second concept in our search strategy was Iraq. Again, we comprehensively searched the literature, and consulted with content experts and a medical librarian, in order to identify as many possible terms for relevant place names and geographic features in Iraq. We also expanded the concept to include the Persian (Arab) Gulf, and terminology related to the Gulf War (1990) and the 2003 US invasion.

3.4.3 Databases and Search Syntax: Academic literature

After developing each concept, they were translated into a syntax appropriate for searching the Medline medical database. Medline is an academic bibliographic database for the life-sciences (particularly medicine), created and maintained by the U.S. National Library of Medicine (NLM 2018). It currently contains more than 25 million journal references, dating back to 1966 (NLM 2018). Due to its sheer volume of references, as well as its unique indexing system of Medical Search Headings, Medline is considered the premier biomedicine bibliographic database (Aagaard, Lund et al. 2016). For systematic reviews conducted by the Cochrane Collaboration, developing a search in Medline is a requirement (Higgins and Green 2011).

To develop the search for Medline every relevant term for a single concept was searched as keyword, connected through the Boolean operator "OR". This technique broadened the search strategy to make it more sensitive. Next, the Medline MeSH (Medical Search Headings) library and tree-structure was thoroughly browsed in order to identify appropriate indexing terms. Each relevant MeSH term was also incorporated into the search syntax with "OR". MeSH terms were also searched as key words. Once both concepts had been built in Medline search syntax, they were combined through the Boolean operator "AND". Searches were further limited to human studies only, and results were restricted to publications between the years of 1990-2018. The year 1990 was selected as a limiting factor in the search strategy because weaponized metallic uranium was not introduced into the environment in Iraq until the first Gulf War (which began in August 1990) (Katz 2014), and thus any publications prior to that year would not be relevant to our study. There were no language restrictions in the search strategy.

One of the highlighted differences between a *systematic review* and a *narrative review* is the range of sources used to identify relevant studies (Higgins and Green 2011). Searching one bibliographic academic database alone is not sufficient, and even Medline, the largest health-related bibliographic academic database, has been shown to typically capture only 30-80% of the relevant studies in a systematic review (Dickersin, Scherer et al. 1994, Higgins and Green 2011).

When our search strategy for Medline had been finalized, we translated it into the appropriate syntax for five additional electronic academic databases: Embase, PubMed, Scopus, Toxline, and Iraqi Academic Scientific Journals (IASJ). With the assistance of a medical librarian (Aida Farha), these databases were selected because of their established prevalence in systematic reviews in the health sciences, their massive

body of indexed epidemiological literature, and (in the case of Toxline and IASJ) their specific relevance to the research topic.

Embase and PubMed, like Medline, are large academic, bibliographic databases for biomedical research. Embase currently contains over 32 million references and uses a unique indexing system called EMTREE (similar to MeSH) (2017). While Medline has a larger archive of US produced biomedical research, Embase contains a larger archive of European produced biomedical research, and the two databases have little overlap (Wong, Wilczynski et al. 2006). Scopus is the world's largest academic bibliographic database, containing over 71 million records, although not exclusively from the medical discipline (Elsevier 2018). Toxline contains 4 million records relevant to the fields of toxicology and environmental health and is maintained by US National Library of Medicine (like Medline) (NLM n.d.). Although much smaller than other academic databases used in this SR, searches of Toxline are widely recognized as mandatory for SRs in evidence-based toxicology (Hoffmann, de Vries et al. 2017). The IASJ database was launched in 2012 by the Ministry of Higher Education & Scientific Research of Iraq, and currently contains nearly 136,000 records of journal articles produced by Iraqi academic research institutions (IASJ 2012, IASJ 2018).

Results from all six databases, in the form of bibliographic references, were either downloaded or manually entered into an EndNote library. The "remove duplicates" function was then used to remove duplicate references that had been captured by multiple databases. This function, while systematic and efficient, is also imperfect and occasionally fails to detect duplicate references, so duplicates were also found and removed during the eligibility screening process. The exact search strategies for each academic database, date that each search was run, and exact number of results

from each search are provided in **Table 5**.

Table 5. Search strategies for each selected academic bibliographic database

Database	**MEDLINE** Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, 1946 to May 11, 2018
Search	(exp URANIUM COMPOUNDS/ or exp URANIUM/ or exp RADIOLOGIC HEALTH/ or THORIUM/ or PLUTONIUM/ or PROTACTINIUM/ or exp THORIUM COMPOUNDS/ or (uranium* or diuranium* or triuranium* or DU or "U(VI)" or "U(IV)" or U-235 or U235 or U-238 or U238 or Qmetal* or (Q adj metal*) or depletalloy* or (deplet* adj alloy*) or uranyl or radiation* or radioactiv* or radioisotop* or radionuclide* or radiologic* or dosimet* or ((gamma* or beta* or alpha* or nuclear) adj3 (ray? or radiation? or emitt* or emission* or decay*)) or plutonium* or thorium* or protactinium*).mp.) AND (exp IRAQ/ or exp IRAQ WAR, 2003-2011/ or exp GULF WAR/ or (Iraq* or (operation* adj2 ((new adj dawn*) or freedom*)) or (gulf adj2 (war* or Arab* or Persian*)) or (operation* adj2 (desert* adj (storm* or shield*))) or mosul* or Falluja* or Al-Anbar* or alanbar* or Anbar* or Babil* or Baghdad* or Al-Basra* or Albasra* or Basra* or ((Dhi or Thi*) adj Qar) or Al-Qadisiy* or Alqadisiy* or Qadisiy* or Diyala* or Dohuk* or Erbil* or Halabja* or Karbala* or Kirkuk* or Maysan* or Al-Muthan* or almuthan* or Muthan* or Najaf* or Ninev* or Saladin* or Sulaymaniy* or Wasit* or kurd*).mp.) AND (1990:2018.(sa_year).) NOT (Animals/ not (Animals/ and Humans/))
Date Run	11 May 2018
Results	309
Date Rerun	13 December 2018
New Results	14
Database	**Embase**
Search	('uranium'/exp OR 'uranium derivative'/exp OR 'radiation and radiation related phenomena'/exp OR 'thorium'/exp OR 'plutonium'/exp OR 'protactinium'/exp OR 'thorium derivative'/exp OR uranium*:ab,ti OR diuranium*:ab,ti OR triuranium*:ab,ti OR du:ab,ti OR 'u(vi)':ab,ti OR 'u(iv)':ab,ti OR 'u-235':ab,ti OR u235:ab,ti OR 'u-238':ab,ti OR u238:ab,ti OR qmetal*:ab,ti OR ((deplet* NEAR/2 alloy*):ab,ti) OR uranyl:ab,ti OR radiation*:ab,ti OR radioactiv*:ab,ti OR radioisotope*:ab,ti OR radionuclide*:ab,ti OR radiological*:ab,ti OR dosimet*:ab,ti OR plutonium*:ab,ti OR thorium*:ab,ti OR protactinium*:ab,ti OR (((gamma* OR beta* OR alpha* OR nuclear) NEAR/3 (ray* OR radiation* OR emitt* OR emission* OR decay*)):ab,ti)) AND ('iraq'/exp OR 'iraqi'/exp OR 'iraqi kurdistan'/exp OR 'persian gulf'/exp OR iraq*:ab,ti OR ((operation* NEAR/2 new*

	NEAR/2 dawn*):ab,ti) OR ((operation* NEAR/2 freedom*):ab,ti) OR ((gulf NEAR/2 war*):ab,ti) OR ((gulf NEAR/2 arab*):ab,ti) OR ((gulf NEAR/2 persian*):ab,ti) OR ((operation* NEAR/2 desert* NEAR/2 storm):ab,ti) OR ((operation* NEAR/2 desert* NEAR/2 shield*):ab,ti) OR mosul*:ab,ti OR falluja*:ab,ti OR 'al-anbar*':ab,ti OR alanbar*:ab,ti OR anbar*:ab,ti OR babil*:ab,ti OR baghdad*:ab,ti OR 'al-basra*':ab,ti OR albasra*:ab,ti OR basra*:ab,ti OR ((dhi* NEAR/2 qar):ab,ti) OR ((thi* NEAR/2 qar):ab,ti) OR 'al-qadisy*':ab,ti OR alqadisy*:ab,ti OR qadisy*:ab,ti OR diyala*:ab,ti OR dohuk*:ab,ti OR erbil*:ab,ti OR halabja*:ab,ti OR karbala*:ab,ti OR kirkuk*:ab,ti OR maysan*:ab,ti OR 'al-muthan*':ab,ti OR almuthan*:ab,ti OR najaf*:ab,ti OR ninev*:ab,ti OR saladin*:ab,ti OR sulaymaniy*:ab,ti OR wasit*:ab,ti OR kurd*:ab,ti) AND [1990-2018]/py NOT ([animals]/lim NOT [humans]/lim)
Date Run	11 May 2018
Results	394
Date Rerun	13 December 2018
New Results	65
Database	**PubMed**
Search	(((iraq[mesh]) OR (iraq war, 2003-2011[mesh]) OR (gulf war[mesh]) OR Iraq*[tw] OR operation new dawn*[tw] OR operation iraqi freedom[tw] OR gulf war*[tw] OR persian gulf*[tw] OR arab gulf*[tw] OR operation desert storm*[tw] OR operation desert shield*[tw] OR mosul*[tw] OR Falluja*[tw] OR Al-Anbar*[tw] OR alanbar*[tw] OR Anbar*[tw] OR Babil*[tw] OR Baghdad*[tw] OR Al-Basra*[tw] OR Albasra*[tw] OR Basra*[tw] OR dhiqar*[tw] OR thiqar*[tw] OR dhi-qar*[tw] OR thi-qar*[tw] OR Al-Qadisiy*[tw] OR Alqadisiy*[tw] OR Qadisiy*[tw] OR Diyala*[tw] OR Dohuk*[tw] OR Erbil*[tw] OR Halabja*[tw] OR Karbala*[tw] OR Kirkuk*[tw] OR Maysan*[tw] OR Al-Muthan*[tw] OR almuthan*[tw] OR Muthan*[tw] OR Najaf*[tw] OR Ninev*[tw] OR Saladin*[tw] OR Sulaymaniy*[tw] OR Wasit*[tw] OR kurd*[tw]) AND ((uranium[mesh]) OR (uranium compounds[mesh]) OR (radiologic health[mesh]) OR (thorium[mesh]) OR (thorium compounds[mesh]) OR (plutonium[mesh]) OR (protactinium[mesh]) OR (uranium*[tw] OR uranyl*[tw] OR plutonium*[tw] OR thorium*[tw] OR protactinium*[tw] OR qmetal*[tw] OR depletalloy*[tw] OR q-metal*[tw] OR deplete-alloy*[tw] OR radiation*[tw] OR du[tw] OR u235[tw] OR u238[tw] OR u-235[tw] OR u-238[tw] OR radiologic*[tw] OR radioactiv*[tw] OR radioisotop*[tw] OR radionuclide*[tw] OR dosimet*[tw] OR gamma-ray*[tw] OR gamma-emit*[tw] OR gamma-emission*[tw] or gamma-decay*[tw] OR beta-ray*[tw] OR beta-emit*[tw] OR beta-emission*[tw] OR beta-decay*[tw] OR alpha-ray*[tw] or alpha-emit*[tw] OR alpha-emission*[tw] OR alpha-decay*[tw] OR nuclear-ray*[tw] or nuclear-emitt*[tw] or nuclear-emission*[tw] or nuclear-decay*[tw]))) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND

	"Humans"[Mesh])) AND ("1990/01/01"[PDAT] : "2018/12/31"[PDAT])
Date Run	11 May 2018
Results	282
Date Rerun	13 December 2018
New Results	8
Database	**Scopus**
Search	TITLE-ABS-KEY("Iraq*" OR (Gulf W/2 War*) OR ((Persia* or Arab*) W/2 Gulf) OR (operation* W/2 new* W/2 dawn*) OR (operation* W/2 freedom*) OR (operation* W/2 desert* W/2 storm*) OR (operation* W/2 desert* W/2 shield*) OR mosul* or Falluja* or *Anbar* or Babil* or Baghdad* or *Basra* or ((Dhi or Thi*) W/2 Qar) or *Qadisiy* or Diyala* or Dohuk* or Erbil* or Halabja* or Karbala* or Kirkuk* or Maysan* or *Muthan* or Najaf* or Ninev* or Saladin* or Sulaymaniy* or Wasit* or kurd*) AND TITLE-ABS-KEY(*uranium* OR thorium* OR plutonium* OR protactinium* OR DU OR "U(VI)" OR "U(IV)" OR U235 OR U-235 OR U238 OR U238 OR qmetal* OR q-metal* or depletalloy* OR (deplet* W/2 alloy*) or uranyl or radiation* or radioactiv* or radioisotop* or radionuclide* or radiologic* or dosimet* or ((gamma* or beta* or alpha* or nuclear) w/3 (ray* or radiation* or emitt* or emission* or decay*))) AND PUBYEAR > 1990
Date Run	11 May 2018
Results	1,155
Date Rerun	13 December 2018
New Results	86
Database	**TOXLINE**
Search	((uranium OR "uranium 238" OR 7440-61-1 [rn]) OR uranyl OR plutonium* OR thorium* OR protactinium* OR qmetal* OR depletalloy* OR "q-metal" OR "deplete-alloy" OR radiation* OR du OR u235 OR u238 OR "u-235" OR "u-238" OR radiologic* OR radioactiv* OR radioisotop* OR radionuclide* OR dosimet* or “alpha-ray” or “alpha ray” or “alpha-emitter” OR “alpha emitter” OR “alpha-emission” OR “alpha emission” OR “alpha-decay” or “alpha decay” or “beta-ray” or “beta ray” or “beta-emitter” or “beta emitter” or “beta-emission” or “beta emission” or “beta-decay” or “beta-decay” or “gamma-ray” or “gamma ray” or “gamma-emitter” or “gamma emitter” or “gamma-emission” or “gamma emission” or “gamma-decay” or “gamma decay” or “nuclear-ray” or “nuclear ray” or “nuclear-emitter” or “nuclear emitter” or “nuclear-emission” or “nuclear emission” or “nuclear-decay” or “nuclear decay”) AND (iraq* OR "gulf war" OR "persian gulf" OR "arab gulf" OR "desert storm" OR "desert shield" OR "operation iraqi freedom" OR "operation new dawn" OR mosul* OR falluja* OR al-anbar* OR alanbar* OR anbar* OR babil* OR baghdad* OR al-basra* OR albasra* OR basra* OR dhi-qar OR thi-qar OR dhiqar OR thiqar OR al-qadisiy* OR alqadisiy* OR qadisiy* OR diyala* OR

	dohuk* OR erbil* OR halabja* OR karbala* OR kirkuk* OR maysan* OR al-muthan* OR almuthan* OR muthan* OR najaf* OR ninev* OR saladin* OR sulaymaniy* OR wasit* OR kurd*) AND 1990:2018 [yr]
Date Run	11 May 2018
Results	440
Date Rerun	13 December 2018
New Results	22
Database	**Iraqi Academic Scientific Journals**
Search	(all:Uranium* all:or all:U-235 all:or all:U-238 all:or all:U235 all:or all:U238) Publication Year: 1990 to 2018
Date Run	14 May 2018
Results	198
Date Rerun	13 December 2018
New Results	10

3.4.4 Databases and Search Syntax: Grey literature

In addition to academic peer-reviewed literature, grey literature is increasingly becoming an important part of SR search strategies (Blackhall 2007, Mahood, Van Eerd et al. 2014). The term *grey literature* entered into use in the 1920's and can be defined as research that is "not available through standard distribution means, no standard bibliographic controls, not peer-reviewed, ephemeral and historically difficult to find" (Tillett and Newbold 2006, Mahood, Van Eerd et al. 2014). Grey literature resources can include dissertations, conference proceedings, reports by governments or NGO's, or research published outside of traditional academic institutions such as magazines or websites.

Traditionally, the inclusion of grey literature has been considered controversial, because the evidence presented in a grey literature resource may not have undergone the same rigorous, critical development, examination, and review process as an academic peer-reviewed publication (Benzies, Premji et al. 2006). However, as SRs

have gained prominence in EBM, and their methodological requirements have become more sophisticated, the importance of including grey literature has become undeniable (Pappas and Williams 2011, Paez 2017). Today, the Cochrane Collaboration requires a search of unpublished studies in their methodology, and encourages the inclusion of unpublished studies in their SRs (Benzies, Premji et al. 2006, Higgins and Green 2011). This is because publication bias (the tendency to only publish studies with statistically significant results) may lead to the exclusion of relevant evidence from peer-reviewed academic journals, and therefore SRs that only use published data may generate erroneous results (McAuley, Tugwell et al. 2000, Conn, Valentine et al. 2003, Benzies, Premji et al. 2006).

It is also conceivable that for a politically-charged topic such as the health impacts of depleted uranium, specific authors or research findings could be black-balled from the academic literature for ideological reasons (Fahey 2004). According to a report produced by the Norwegian peace organization IKV PAX Christi, the grey literature is rich with studies and cases-reports concerning the health impacts of DU, which deserve a thorough review and examination when assessing the evidence for this particular topic (Zwijnenburg 2013).

Therefore, after developing and implementing the search strategy for six academic bibliographic databases we searched five additional sources for grey literature publications: WHO Digital Library, UNEP Knowledge Repository, IAEA Scientific and Technical Publications, Google Scholar, and ProQuest Global Dissertations and Theses. These sources were identified and selected with the assistance of a medical librarian (Aida Farha). Their selection was also determined by a prior review of the

literature, which noted the international agencies that have conducted post-war research and evaluations in Iraq.

The development of search strategies for grey literature sources was less straightforward than for the academic bibliographic databases. This is partially due to the fact that guidelines or methods for searching grey literature are not widely reported or available (Mahood, Van Eerd et al. 2014). Even though including grey literature is often a feature of SRs, peer-reviewed academic SRs usually do not have the space to report their methods in journal articles (Mahood, Van Eerd et al. 2014).

Ultimately, we followed the guidelines of Mahood and colleagues (2014) in developing the search strategies for our grey literature sources (Mahood, Van Eerd et al. 2014). The Mahood et al (2014) grey literature guidelines call for constructing three types of searches: a full search (the search used for academic bibliographic databases), a modified search (with fewer terms, specifically without indexing terms), and a two-term simple search. Not all of the grey literature sources accepted elaborate search strategies (using techniques such as truncation or even Boolean operators), and so in some cases, a modified search or two-term simple search had to be applied. A detailed description of search functionalities for each grey literature source, and process for search strategy development, are provided in **Appendix I**.

Results from the grey literature sources were either downloaded or manually entered into an EndNote library (a second library, separate from the library used to manage results from the first set of academic databases), and duplicates were removed using a combination of the "remove duplicates" function in EndNote and manual removal. The exact search strategies for each grey literature source, date that each

search was run, and exact number of results from each search are provided in **Table 6.**

Table 6. Search strategies for each selected grey literature source

Database	**ProQuest Dissertations and Theses Global**
Search	TI,AB,SU((uranium* OR uranyl OR plutonium* OR thorium* OR protactinium* OR qmetal* OR depletalloy* OR "q-metal" OR "deplete-alloy" OR radiation* OR du OR u235 OR u238 OR "u-235" OR "u-238" OR radiologic* OR radioactiv* OR radioisotop* OR radionuclide* OR dosimet* or “alpha-ray” or “alpha ray” or “alpha-emitter” OR “alpha emitter” OR “alpha-emission” OR “alpha emission” OR “alpha-decay” or “alpha decay” or “beta-ray” or “beta ray” or “beta-emitter” or “beta emitter” or “beta-emission” or “beta emission” or “beta-decay” or “beta-decay” or “gamma-ray” or “gamma ray” or “gamma-emitter” or “gamma emitter” or “gamma-emission” or “gamma emission” or “gamma-decay” or “gamma decay” or “nuclear-ray” or “nuclear ray” or “nuclear-emitter” or “nuclear emitter” or “nuclear-emission” or “nuclear emission” or “nuclear-decay” or “nuclear decay”) AND (iraq* OR "gulf war" OR "persian gulf" OR "arab gulf" OR "desert storm" OR "desert shield" OR "operation iraqi freedom" OR "operation new dawn" OR mosul* OR falluja* OR al-anbar* OR alanbar* OR anbar* OR babil* OR baghdad* OR al-basra* OR albasra* OR basra* OR dhi-qar OR thi-qar OR dhiqar OR thiqar OR al-qadisiy* OR alqadisiy* OR qadisiy* OR diyala* OR dohuk* OR erbil* OR halabja* OR karbala* OR kirkuk* OR maysan* OR al-muthan* OR almuthan* OR muthan* OR najaf* OR ninev* OR saladin* OR sulaymaniy* OR wasit* OR kurd*)) AND YR(1990-2018)
Date Run	30 August 2018
Results	50
Date Rerun	20 December 2018
New Results	2
Database	**Google Scholar**
Search	Allintitle: Uranium Iraq Publication Year: 1990-2018
Date Run	30 August 2018
Results	110
Date Rerun	20 December 2018
New Results	2
Database	**IAEA Scientific and Technical Publications**
Search	Search: Uranium Publication Year: 1990-2018 Search: Iraq Search: Iraqi

Date Run	10 July 2018
Results	104
Date Rerun	20 December 2018
New Results	3
Database	**WHO Institutional Repository for Information Sharing**
Search	Iraq* AND Uranium
Date Run	19 August 2018
Results	40
Date Rerun	20 December 2018
New Results	0
Database	**UNEP Knowledge Repository**
Search	Iraq
Date Run	**29 August 2018**
Results	**22**
Date Rerun	20 December 2018
New Results	5

It should be noted that besides the results obtained from database searches, additional studies were identified by screening the reference lists of included studies by hand, tracking citations of included studies backwards and forwards, and consulting with content experts. Each of the database searches were re-run just before the final analyses and new results were screened for any additional relevant studies (see above **Table 5** and **Table 6**).

3.5 Eligibility screening and study selection

Following the implementation of the search strategy, the next step in an SR involves the application of the predetermined eligibility criteria to the captured references during a systematic screening process (Frampton, Livoreil et al. 2017). The screening process has two phases. First, a title and abstract screening phase, and second, a full-text screening phase. To minimize selection bias, the screening process is not

conducted by a single reviewer (McDonagh, Peterson et al. 2013, Frampton, Livoreil et al. 2017). Rather, every individual reference is screened by at least two reviewers separately, during both screening phases. For this SR, three reviewers were involved in eligibility screening, using multiple reference libraries in EndNote.

3.5.1 Phase 1: Title and abstract screening

Prior to initiating the title and abstract screening, calibration exercises was carried out, in order to test the screening protocol and to ensure a high level of agreement between the three reviewers. After completing the calibration exercises, titles and abstracts were screened by the primary reviewer (Shelby Surdyk) to identify studies that meet the inclusion criteria. Simultaneously, the entire set of captured studies were divided in half, and each of the other two reviewers were assigned one half of the set to screen independently. Any study judged as eligible by at least one reviewer will be eligible for full-text screening. The title and abstract screening form is provided in **Appendix 2**.

In this SR, screening the titles and abstracts of references captured after searching the first set of academic databases was conducted during the months of July and August 2018, while title and abstract screening of references captured during the grey literature search was conducted during the months of September and October 2018.

3.5.2 Phase 2: Full-text screening

To obtain full-texts for the included references from the first set of databases, the ‘get full-text’ feature in EndNote was used. This feature was able to retrieve full-

text PDFs or URLs for 54 of the included references. The 'export references' feature in EndNote was then used to create an Excel spreadsheet listing all references for which full-texts still needed to be obtained. This spreadsheet was shared with librarians at Saab Medical Library at the American University of Beirut, who used institutional privileges and inter-library loan options to retrieve the remaining full-texts. Once retrieved, the SML librarians shared all PDFs with the primary reviewer (Shelby Surdyk), who downloaded them and linked them to their appropriate references in the EndNote library.

Like the title and abstract screening phase, calibration exercises were carried out among the reviewers following a pre-specified protocol prior to the commencement of full-text eligibility screening. The full text screening form is provided in **Appendix 3**.

After the full-text calibration exercises have been completed, full-texts of included studies were independently assessed in duplicate by two reviewers (Shelby Surdyk & Moustapha Itani). Unlike the title and abstract screening phase, during the full-text screening phase, reviewers must document their reasons for excluding full-texts (Meline 2006). Using the full-text screening protocol, reviewers will independently record their reasons for exclusion of full-texts in an Excel spreadsheet. After each full-text had been screened for eligibility (independently, in duplicate), the two reviewers met to discuss disagreements for inclusion/exclusion, as well as disagreements over the justifications given for exclusion of full-texts. In cases of disagreement between the two reviewers, input from a third reviewer was sought (Lara Kahale or Rima R. Habib).

3.6 Data Abstraction

A standardized, pre-piloted form was used to extract data from the included studies for quality assessment and evidence synthesis **(Table 7).** The items included in the data abstraction form can be divided into two types of data: study characteristic items and risk of bias items. The latter were derived from the Navigation Guide's Risk of Bias tool developed for the assessment of human observational studies (Johnson, Sutton et al. 2014), while study characteristic items were selected by the primary author of this study (Shelby Surdyk) after a review of the literature and consultation with experts on systematic review methodology (Lara Kahale).

During data abstraction the primary reviewer (Shelby Surdyk) abstracted data, following the established protocol, for each included study. A second reviewer (Moustapha Itani) simultaneously, and independently, abstracted data from each eligible full-text. This ensured that each eligible full-text underwent data abstraction by two reviewers, independently. The two reviewers then met to resolve disagreement and harmonize the dataset for each of the abstracted studies. Ultimately, a master table (meta-synthesis) was created which included the abstracted data for each included study.

Table 7. Items included in the data abstraction form

Study Characteristics	Risk of Bias
Participants - Target population - Total number of study participants - Characteristics of participants (age, gender, etc.) *Exposure* - Type of exposure assessed *Comparator* - Characteristics of comparator/controls *Outcome* - Type of health outcome assessed - Method of health outcome assessment - Time of health outcome measurement *Design* - Year of publication - Setting - Study Design *Status* - Published or unpublished study *Findings* - Association measured - Major finding/conclusions of study Notes	*Recruitment* - Recruitment strategy for participants - Recruitment strategy for comparator/controls - Response Rate *Blinding* - Blinding measures in place *Confounding* - Confounding variables measured/assessed *Exposure assessment* - Exposure assessment methods - Time of exposure measurement - Location of exposure measurement *Incomplete outcome data* - Strategy for addressing missing outcome data *Selective reporting* - Evidence of selective outcome reporting Other sources of methodological bias Financial conflict of interest

3.7 Risk of Bias assessment

One of the situations in which a systematic review is considered necessary is when a large body of evidence contains contradictory findings, thus making interpretation of the evidence challenging (Grant and Booth 2009). One possible explanation for disagreement between individual study results is the presence of bias in

one or more relevant study; that is to say, flaws in the internal validity of one or more studies (Steckler and McLeroy 2008). A bias, according to the Cochrane Systematic Reviews Handbook, is a systematic (nonrandom) error in the results of a study caused by a methodological flaw, effecting the magnitude or direction of results (Higgins and Green 2011). Assessing studies for such flaws (or limitations) can inform a determination of whether a causal relationship can be interpreted from a finding of association or statistical correlation (Steckler and McLeroy 2008).

After capturing all relevant studies and abstracting their data, the methodology of each individual study in our systematic review must be assessed for sources of bias. Because the presence of a methodological flaw in an individual study does not necessarily mean that the study's results are erroneous, a systematic review does not assess whether individuals study results are biased, but rather whether there is a *risk* of bias in the study design (Higgins and Green 2011).

Risk of bias for individual studies will be assessed using the instrument developed by Woodruff and Sutton (2014) for the Navigation Guide Systematic Review Methodology, included in **Appendix 4**, with amendments. This instrument is made up of eight domains for which the possibility of bias is assessed: recruitment strategy, confounding, exposure assessment, incomplete outcome data, selective outcome reporting, conflict of interest, other sources of bias (Johnson, Sutton et al. 2014). For each domain, reviewers can document the risk of bias for each individual study as "Low risk of bias", "Probably low risk of bias", "Probably high risk of bias", "High risk of bias", or "Not Applicable" following prespecified criteria (Johnson, Sutton et al. 2014).

The Guidelines and Standards for Evidence Synthesis in Environmental Management, produced by the Collaboration for Environmental Evidence (CEE), argue

that given the diversity of 'study systems' forming the body of evidence relevant to questions of environmental health, no single instrument can be implemented without amendments in an SR of an environmental health topic. Likewise, Shamliyan and colleagues have argued that there is no 'gold standard' to assess internal validity (risk of bias) in observational studies (Shamliyan, Kane et al. 2010). Therefore, although the risk of bias assessments implemented in this SR will largely follow the Navigation Guide's instrument, key pre-specified amendments (or elaborations) of that tool will also guide our assessments. Namely, study designs that employ a geographical comparison within Iraq as a means of comparing weaponized uranium exposure (e.g., an exposed city versus and unexposed city) will receive a judgement of "probably low risk of bias" in the recruitment domain, as long as the study is free of suggestion of differences in recruitment strategy employed in the cities of comparison. However, if, in a geographic comparison, the study authors do not provide evidence that the compared cities do possess different levels of weaponized uranium contamination, then under the domain of exposure assessment, the study will be judged to have a "high risk of bias" in that domain. In study designs that employ a historic control (either data published on a past population sample, or data published on a population outside of Iraq), the study will be judged "high risk of bias" in the domain of recruitment, unless recruitment strategies for the historic control population are reported and are reasonably comparable to the recruitment strategies employed among contemporary cases. Ecological (time trend) or cross-sectional studies that measure an outcome on the population level (such as cancer or birth defect incidence), and use time (year) as a measure of uranium exposure (i.e., data from years prior to 1991 or 2003 represent

unexposed time frames, and data from years after 1991 or 2003 represent exposed time frames), will be judged to have "low risk of bias" in the domain of exposure.

Regarding the domain of confounding, studies in this SR will be judged "low risk of bias" if they account for age and sex in participants when using uranium concentration in human tissues as a measure of exposure, because uranium concentrations have been found to vary significantly with age and sex (Alaani, Tafash et al. 2011). Additionally, to receive a judgment of "low risk of bias" for confounding, the study must be must either be free of suggestion that other important confounders, such as occupation, that could influence the outcomes assessed, or must control for those important variables. In studies that measure birth outcomes, maternal age and consanguinity will be considered important confounding variable which must be accounted for, in order for a study to be judged "low risk of bias" in that domain.

When implementing risk of bias assessments in this SR, two reviewers will independently make and document risk of bias for each individual study across all eight domains. The two reviewers will then meet to compare their assessment. If the two reviewers disagree on risk of bias determination for any domain of any study, a third reviewer will be asked to assess the risk of bias. If, following further discussion, the three reviewers are not able to come to a consensus regarding the risk of bias determination for any domain, then the more conservative determination will be adopted. Results from risk of bias assessments will be reported in tabular form for each individual study.

Calibration exercises will be carried out with all three reviewers prior to the commencement of the risk of bias assessment phase using the Navigation Guide risk of bias instrument. Results of the risk of bias assessments will inform the data synthesis

phase of the review.

3.8 Data Synthesis

Traditionally, in SRs of interventions using RCTs, evidence is synthesized quantitatively in the form of a meta-analysis. When the Navigation Guide's methodology was implemented to determine the effects of exposure to perfluorooctanoic acid (PFOA) on fetal development, the findings from 10 human observational studies were synthesized in a meta-analysis (Johnson, Sutton et al. 2014). However, a meta-analysis was not planned for this SR, as we anticipated that the range of different outcomes measured across the small number of existing observational studies would limit the scope and preclude the possibility of a meta-analysis.

Instead, this SR will produce a *narrative synthesis*, following guidelines produced by the Center for Reviews and Dissemination at the University of York (Popay, Roberts et al.). At its core, a narrative synthesis is a story-telling technique, tailored to the realm of health policy and practice. For SR's on the *effects* of intervention (or exposure), a narrative synthesis must contain four elements: (a) Theoretical model of how the exposure manifests as health impact, why and for whom, (b) Preliminary synthesis, (c) Exploration of relationships in the data, (d) Assessment of the robustness of the synthesis product (Popay, Roberts et al.). As such, a narrative synthesis is a type of evidence synthesis that differs from a *narrative review*. Unlike traditional literature reviews (e.g. narrative reviews), a narrative synthesis aims to be systematic and transparent in its approach.

For this systematic review, the mechanism of toxicity of uranium (presented in Chapter II - Background) functions as the theoretical model within our narrative

synthesis. The preliminary synthesis (presented in Chapter IV – Results), organizes the findings of included studies by outcome, and summarizes the direction of associations and size of effects (if data is available) for each outcome. In our exploration of relationships in the data (presented in Chapter V – Discussion), we critically appraise the findings of included studies in relation to their study characteristics and risk of bias assessments. Finally, the robustness of the synthesis product refers to the strength of evidence for both the direction and size of effect, as well as generalizability for other populations and other contexts (i.e. external validity). Our assessment of the strength of evidence is presented in Chapter V – Discussion.

Our narrative synthesis will seek to answer the following questions across the body of evidence: Are the results consistent across all the studies? If not, can the results be explained by other factors? Are there any important confounding variables that are routinely overlooked? Are there trends with time (year of study) or location across studies? Is there agreement between high and low quality studies?

3.9 Protocol registration

PROSPERO (the international prospective register of systematic reviews) is an online database of SR protocols relevant to the fields of public health and social welfare. Launched in 2011, the mission of PROSPERO is to increase the transparency, validity, and impact of health-related SRs by providing a platform where *a priori* SR methods can be published and accessed for free (Moher, Shamseer et al. 2015). The registration form includes 22 mandatory and 18 optional fields covering every aspect of an SR's methodology including study objectives, context, information sources, search strategy, inclusion/exclusion criteria, screening procedures, data abstraction procedures,

individual study quality assessment, and strategy for evidence synthesis. To date, more than 20,000 SR protocols have been published on PROSPERO, making it the world's largest prospective SR registry (Andrade, Pereira et al. 2017). While protocols published on PROSPERO have not necessarily undergone a peer-review process, publication on the registry holds SR authors accountable to their *a priori* methodology, which can be referenced in a manuscript that is submitted to a peer-reviewed journal for publication when the SR has been completed.

Our SR protocol was published on PROSPERO on September 12th, 2018 (registration number: CRD42018108225).

3.10 PRISMA Statement

PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) Checklist was developed in 2009 as an advancement and improvement of the 1999 QUOROM (Quality Of Reporting Of Meta-analysis) Statement (Liberati, Altman et al. 2009). Use of the PRISMA Checklist is a recommended reporting requirement by the National Toxicology Program (NTP) at the U.S. National Institute of Health for systematic reviews in the field of environmental health (Rooney, Boyles et al. 2014). Therefore, this SR will be reported in tabular form following the PRISMA 2009 Checklist **(Appendix 5).**

CHAPTER IV

RESULTS

4.1 Screening and study selection

Our search of selected academic and grey literature databases retrieved 2,009 unique records. Of those, 210 met our inclusion criteria at the title and abstract screening phase **(Figure 4).** The full text articles for twelve of those records could not be retrieved. The records for all of the unretrievable texts came from our grey literature search and either (a) contained insufficient bibliographic data for tracking the source of the records, or (b) were Master's theses published in Iraqi universities for which the universities did not yet have permission to release the full-text, or did not respond to our request for the full-text. Of the 198 records that underwent full text screening, 21 met our inclusion criteria **(Appendix 6).** By screening the citation lists of included articles, and by tracking their citations in Google Scholar, we identified five additional records that were not captured in our database search. Three content experts were contacted, none of whom were aware of any additional relevant articles. The content experts contacted were: Mozghan Savabieasfahani (University of Michigan), Ross Caputi (University of Massachusetts Amherst), and Wim Zwijnenburg (IKV PAX Christi). No additional records meeting our inclusion criteria were identified during a rerun of our database searches in December 2018. Of the 26 total included articles, three reported the results of two relevant studies, and one article reported the results of three relevant studies. Thus, the final number of studies included in our evidence synthesis was 31 **(Table 8).** In some instances, case and comparison groups overlap across studies published in the same article, and so the studies cannot be said to be independent from

each other.

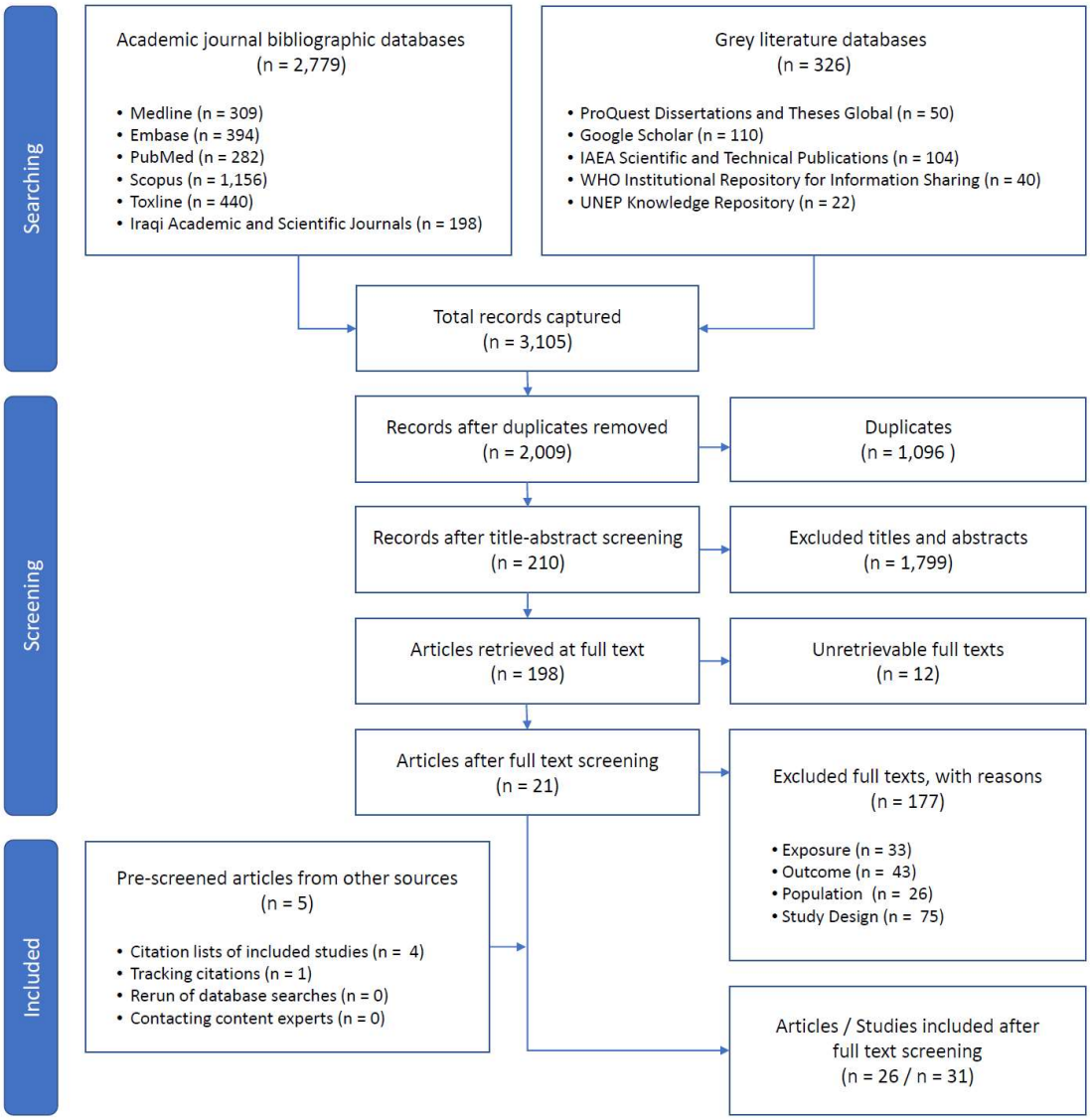

Figure 4. Flow diagram of study selection

Table 8. Summary of study characteristics of human observational studies measuring association between exposure to weaponized uranium and adverse patient-important health outcomes among the Iraqi population

Study ID	Study Design	Study Timeframe	Population/ Location	Sample size	Exposure	Outcome(s)	Statistical test(s)	Results	Funding
Abdul-Wahid (2009)	Case-control	June 2007	Residents of a district in northern Al-Basrah city	Cases = 50 Controls = 50	Place of residence (Exposed = Basrah, Unexposed = Baghdad)	Immune system function (lymphocyte phenotyping: % of cells as lymphocytes in blood sample)	T-test	Cases were found to have lower levels of selected lymphocytes (CD3, CD4, CD8, CD19, and CD56) compared to controls (p-values not reported)	Not declared
Alaani et al (2012)	Case-control	Nov. 2009 – Sept. 2010	Births in Fallujah	Population based	Place of residence (Exposed = Fallujah, Unexposed = Egypt, Kuwait, and UAE, i.e. historical control)	CBD incidence rate (number of infants born with CBD per 1000 live births in population)	No statistical test	CBD incidence in Fallujah for the 11 month period was reported to be between 48-144/ 1000 live births. This rate is many times higher that CBD incidence reported for other (unexposed) Arab countries (Giza, Egypt 31.7, Kuwait 12.5, UAE 7.9)	The Children's Health Foundation (London), the International Foundation for Research on Radioactivity Risk (Stockholm)
Alaani et al (2011a)	Case-control	2009-2010	Parents who gave birth to children with CBD at Fallujah General Hospital	Cases = 25 Controls = 99	Uranium concentration in hair (U $mg \cdot kg^{-1}$), ICPMS	Infant with CBD	Mann-Whitley U-Wilcox non-parametric test	The Fallujah cohort (cases) were found to have significantly higher levels of uranium in hair samples (0.16 U $mg \cdot kg^{-1} \pm$ 0.11 SD) than the control population (historical control) in Southern Israel (0.062 U $mg \cdot kg^{-1}$) (p=0.016)	The Joseph Rowntree Charitable Trust, the Cancer and Birth Defects Foundation (London, UK), and the International Foundation for Research on Radiation risk

									(Stockholm, Sweden)
Alaani et al (2011b)	Case-control	2009-2010	Mothers who gave birth to children with CBD at Fallujah General Hospital	Cases = 6 Controls = 114	Uranium concentration along length of hair ($mg \cdot kg^{-1}$per length interval), ICPMS	Infant with CBD	No statistical test	Uranium concentrations in long-hair samples from the Fallujah cases (0.26 U $mg \cdot kg^{-1} \pm$ 0.09 SD) were found to be more that 2 SD from the mean for control population (historical control) in Northern Sweden (0.057 U $mg \cdot kg^{-1} \pm$ 0.065 SD), uranium content does not fall along the length of hair in Fallujah cases as compared to Swedish controls, indicating higher exposure among the Fallujah population in the past compared to present	Funding provided by: the Joseph Rowntree Charitable Trust, the Cancer and Birth Defects Foundation (London, UK), and the International Foundation for Research on Radiation risk (Stockholm, Sweden)
Alborz (2013)	Cross-sectional	2010	Residents of Basrah governorate	Households = 6032 Children = 10,714	Place of residence - Self-reported exposure to "warfare contamination" (Exposed = Yes, Unexposed = No)	Child with CBD	Chi-squared	A significantly higher proportion of children with birth defects in Basra (105 out of 383) were found to be living in households that reported exposure to "warfare contamination" than children without birth defects (1349 out of 9547) ($p<0.001$)	UNICEF and AusAID

Al-Hamadany et al (2012a)	Case-control	2009-2010	Residents of Baghdad	Cases = 74 Controls = 14	Uranium concentration in blood samples (ppm), CR-39 fission track detector	Illness (Cases = patients with cancer and mothers of children with CBD, Controls = healthy adults)	T-test	Results comparing predefined cases and controls were not reported; Rather, mean uranium concentrations in blood samples are compared between a portion of the control samples (only those healthy individuals living in uncontaminated areas) (0.11ppm ± 0.009 SE), and the cancer patient samples plus the other controls (0.21 ppm ± 0.01 SE) and the difference was statistically significant ($p<0.05$)	Not declared
Al- Hamadany et al (2012b)	Case-control	2009-2010	Residents of Baghdad	Cases = 74 Controls = 14	Place of residence, health status, or occupation (Exposed = cancer patients, mothers of children with CBDs, employees of the Institute and Hospital of Radiotherapy and Nuclear Medicine, or individuals residing in areas of Baghdad identified by UNEP as contaminated, Unexposed = healthy	Total and Differential W.B.C. Count, Hemoglobin Concentration, neutrophils phagocytic activity, IFN-γ concentrations , IL-2 concentrations	Independent sample t-tests	WBC counts were significantly higher among groups defined as "exposed" and hemoglobin concentrations were significantly lower compared to the group defined as unexposed ($p<0.05$)	Not declared

					individuals residing in areas reported to be free of weaponized uranium)				
Al-Hamzawi et al (2015)	Case-control	N/R*	Residents of Southern Iraqi governorates (Basrah, Muthanna, and Dhi-Qar)	Cases = 24 Controls = 12	Uranium concentration in tissue ($\mu g \cdot kg^{-1}$), CR-39 fission track detector	Cancer (Cases = kidney, breast, stomach, and uterus cancer tissues, Controls = kidney, breast, stomach, and uterus tissues from healthy individuals)	Independent sample t-test	Significant differences in mean uranium concentrations were found between tissues from cancer patients compared to healthy controls for all cancer types: • **Kidney** ($p < 0.001$) Cancer: 6.51 $\mu g \cdot kg^{-1}$ ± 0.20 SD Normal: 4.11 $\mu g \cdot kg^{-1}$ ± 0.38 SD • **Breast** ($p < 0.01$) Cancer: 5.04 $\mu g \cdot kg^{-1}$ ± 0.27 SD Normal: 2.96 $\mu g \cdot kg^{-1}$ ± 0.16 SD, • **Stomach** ($p < 0.01$) Cancer: 5.22 $\mu g \cdot kg^{-1}$ ± 0.22 SD Normal: 3.11 $\mu g \cdot kg^{-1}$ ± 0.29 SD • **Uterus** ($p < 0.01$) Cancer: 4.61 $\mu g \cdot kg^{-1}$ ± 0.32 SD Normal: 2.28 $\mu g \cdot kg^{-1}$ ± 0.51 SD	School of Physics Universiti Sains Malaysia, Research Grant No. 1001/PFIZIK/845012
Al-Hamzawi et al (2014)	Case-control	N/R*	Residents of Southern Iraqi governorates (Basrah, Muthanna, and Dhi-Qar)	Cases = 30 Controls = 30	Uranium concentrations in blood samples (ppb), CR-39 fission track detector	Leukemia (Cases = leukemia patients in selected hospitals,	Independent sample t-test	Uranium concentrations in blood samples from the leukemia patients (2.87 ppb ± 0.11 SD) were found to be significantly higher than those from the healthy group (1.43	Not declared

						Controls = healthy volunteers residing in the same areas as hospitals)		ppb ± 0.07 SD) ($p<0.001$), and uranium concentrations from cases and controls from Basrah were higher than concentrations in blood samples from the other governorates ($p<0.05$)	
Al-Hashimi & Wang (2013)	Ecological: Time trend	1980-2010	Residents of Ninawa Province	Population based	Time period (Unexposed = 1980-1990, Exposed = 1991-2000 and 2001-2010)	Cancer incidence rate ratio (IRR)	Poisson regression analysis	IRR for most cancer types in Ninawa significantly decreased in the second (1991-2000) and third period (2001-2010) compared to the first period (1980-1990) ($p < 0.01$), leukemia increased in the third period (IRR: 0.2152, CI: 0.1976-0.2346) compared to the second period (IRR: 0.1731, CI: 0.1505-0.1990), but not to the first period (IRR: 0.2964, CI: 0.2433-0.3611)	Ministry of Higher Education and Scientific Research/University of Mosul/Iraq
Al-Jobori (2013)	Case-control	N/R*	Cancer patients residing in the South of Iraq	Cases = 9 Controls = 3	Uranium concentration in tissues (CR-39 fission track detector)	Cancer (Cases = samples from kidney, bone, breast, lung and liver cancer patients, Controls = samples from kidney, bone, and breast cancer patients)	No statistical test	Uranium was not detected in tissue samples from any of the non-cancerous controls	Not declared
Al-Rudainy et al (2011)	Ecological: Time trend	2004-2009	Residents of Basrah Governorate	Population based	Time period (Least exposed = 2004, Most exposed = 2009)	Incidence of childhood Leukemia (0-14 years old)	Standard linear regression, test for trend using parameter	Incidence of childhood leukemia did not change over the 6 year study period. Leukaemia rates decreased by 0.123 per 100,000 between 2004-2009, but the test	Not declared

							estimates of regression model	for trend was not significant (p=0.81)	
Al-Rudainy et al (2009)[i]	Ecological: Geographic comparison	2006	Residents of Basrah Governorate	Population based	Place of residence - Locations of DU contaminated sites in Basrah governorate were compiled through a literature and meta-geographic-analysis	Cancer incidence rate by district	Spearman correlation analysis	No statistical correlation was found between level of DU contamination and cancer incidence rate by district (r= -0.01, p= 0.98)	Not declared
Al-Rudainy et al (2009)[ii]	Ecological: Time trend	2003-2007	Residents of Basrah Governorate	Population based	Time period (Least exposed = 2003, Most exposed = 2007)	Incidence of childhood Leukemia (1-14 years old)	No statistical test	Over the 5 years study period, no increase in childhood leukemia incidence was observed.	Not declared
Al-Sabbak et al (2012a)	Ecological: Time trend	1994-2011	Births in Al-Basrah city	Population based	Time period (Unexposed = 1994, Exposed = 2003-2011)	CBD incidence rate (number of infants born with CBD per 1000 live births in population)	No statistical test	The CBD incidence rate in Al-Basrah increased 17-fold between 1994 (1.37 CBD per 1000 live births) and 2003 (23 CBD/1000 live births)	University of Michigan Department of Obstetrics and Gynecology
Al-Sabbak et al (2012b)	Case-control	May – Aug. 2010	Parents who gave birth to children with CBD at Fallujah General Hospital	Cases = 103 Controls = 9	Uranium concentration in hair ($\mu g \cdot kg^{-1}$), ICPMS	Diagnosis of infant at time of delivery at Fallujah General Hospital (Cases =	Independent sample t-test	Uranium concentrations in hair from cases (parents of children with birth defects) and was higher than in controls (parents of healthy children), but the difference was not statistically significant ($p > 0.05$)	University of Michigan Department of Obstetrics and Gynecology

						stillbirths or infants with CBD, Controls = healthy live births)			
Al-Sadoon et al (1999)	Ecological: Time trend	1990-1998	Residents of Basrah	Population based	Time period - Year of congenital anomaly registration (Unexposed = 1990, Exposed = 1991-1998, later years are equated with greater exposure)	CBD incidence	SND test for difference in proportions (z-test)	A significant increase in CBD incidence in Basrah was found between the periods 1991-1994 (2.5 CBDs/1000 live births) and 1995-1998 (4.57 CBDs/1000 live births) (SND=5.37, $p<0.01$)	Not declared
Al-Sahlanee et al (2017)	Cross-sectional	N/R**	Infants born at maternity hospitals in Baghdad	Participants = 50 mother-neonate pairs	Uranium concentration in maternal and umbilical cord blood samples (ppm), CR-39 fission track detector	Infant anthropometric measurements (birth weight, body length, head circumference), determined at time of delivery	Adjusted regression model	Uranium concentrations in maternal blood samples (0.95 ppm ± 0.62 SD) and umbilical cord blood samples (0.68 ppm ± 0.39 SD) were found to be negatively, significantly correlated with the anthropometric measurements (infant birth weight, body length, and head circumference) ($p<0.05$), except for infant umbilical cord blood uranium concentrations and body length (correlation was negative but not significant, $p>0.05$)	Universiti Sains Malaysia, Research grants (304/PFIZIK/6312125, 304/PFIZIK/6313249, and 304/PJJAUH/6313152)
Al-Sahlanee et al (2016)	Case-control	N/R**	Infants born in Baghdad, Dhi-Qar and Basrah.	Participants = 47 mother-neonate pairs	Uranium concentration in maternal and umbilical cord blood	Diagnosis at time of delivery in Baghdad (Hospital of	Independent sample t-tests	Mean uranium concentrations in the maternal and umbilical cord blood samples of deformed infants (2.43 ppb ± 0.89 SD, and 1.99 ppb ± 0.78 SD,	Universiti Sains Malaysia, Research grants (304/PFIZIK/6312125,

					samples (ppb), CR-39 fission track detector	Al-Yarmuk and Hospital of Al-Alwiyah), Basrah (Hospital of Gezwan) and Dih-Qar (Hospital of Al-Shatrah and Hospital of Al-Nasriah), (Cases = infants born dead and deformed, Controls = infants born normal and alive)		respectively) were found to be significantly higher than those samples from normal infants (1.26 ppb ± 0.51 SD, and 0.97 ppb ± 0.38 SD, respectively) ($p<0.05$), samples from Basrah also had significantly higher uranium concentrations than the other two regions (Baghdad and Dhi-Qar)	304/PFIZIK/6313249, and 304/PJJAUH/6313152)
Busby et al (2010a)	Cross-sectional	Jan. 20 - Feb. 20, 2010	Residents of Fallujah	Households = 711 Children = 2,132	Time period - Year of birth (Exposed = births after 2005, Unexposed = births prior to 2005)	Birth-sex ratio (ratio of male births to 1000 female births), as reported by subjects in household survey	A statistical test was reportedly used, but not described	Birth-sex ratio decreased to 0.86 for children born between 2006-2010, compared to 1.182 for children born between 2001-2005, 1.109 for children born between 1996-2000, and 1.010 for children born between 1991-1995; the birth-sex ratio for children born between 2006-2010 was found to differ significantly from the expected ratio	Partially funded by Green Audit, the Joseph Rowntree Charitable Trust, and "was otherwise privately funded"
Busby et al (2010b)	Case-control	Jan. 20 - Feb. 20, 2010	Residents of Fallujah	Households = 711	Place of residence (Exposed = Fallujah, Unexposed =	Infant mortality rate (IMR)	Z-test	IMR in Fallujah between 2006-2010 was four times higher than IMR in Egypt and Jordan ($p < 0.00001$), and nine time higher that the IMR in Kuwait	Partially funded by Green Audit, the Joseph Rowntree Charitable

					Egypt, Jordan, and Kuwait)				Trust, and "was otherwise privately funded"
Busby et al (2010c)	Case-control	Jan. 20 - Feb. 20, 2010	Residents of Fallujah	Households = 711	Place of residence (Exposed = Fallujah, Unexposed = Egypt, Jordan, and Kuwait)	Cancer incidence	Z-test	Relative Risk (RR) for cancer incidence in Fallujah between 2005-2010 compared to Egypt was 4.22 (CI: 2.8 - 6.6, $p < 0.00000001$)	Partially funded by Green Audit, the Joseph Rowntree Charitable Trust, and "was otherwise privately funded"
Hagopian et al (2010)	Ecological: Time trend	1993-2007	Children (0-14 years of age) residing in Basrah governorate	Population based	Time period - Year of leukemia registration (recent years equates with greater weaponized uranium exposure, earlier years with less exposure)	Leukemia incidence among children aged 0-14 years, over three year periods	Standard linear regression	A significant ($p=0.03$) trend of increasing incidence of childhood leukemia in Basrah between 1993-2007 was found; incidence more than doubled over the study period (ratio of 2005–2007 incidence to 1993–1995 incidence=2.7; CI=1.437, 5.124)	University of Washington Puget Sound Partners for Global Health (research and technology grant 26145/RTP2005-8)
Hassan et al (2005)	Ecological: Time trend	1997-2002	Residents of Basrah governorate	Population based	Time period - Year of death or diagnosis (max. exposure = 2002, min. exposure = 1997)	Cancer incidence rate (IR) and mortality rate (MR)	No statistical test reported in study, but a linear regression performed by authors of this SR using reported IR showed a positive trend and moderate effect size (r-	No significant increases in cancer IR or MR were observed in Basrah over the study period.	Not declared

							squared = 0.58)		
Humaidi & Khalaf (2011)	Case-control	Aug. 2005 – Aug. 2009	Bullet wounded Iraqi's in Ramadi	Cases = 196 Controls = 19	Bullet type (Exposed = shot by US or coalition forces, unexposed = shot by other source)	W.B.C. count, hemoglobin concentration, erythrocyte sedimentation ratio, total serum Bilirubin, alkaline phosphates enzyme concentration, serum transferees enzymes concentration, serum Creatinine concentration, blood urea concentration, mitotic index.	ANOVA	There were significant differences ($p<0.05$) between cases and controls for all outcomes measured	Not declared
Mohammad (2016)	Case-control	2007-2009	Breast cancer patients in Baghdad	Cases = 50 Controls = 30	Place of residence (Exposed = Iraq, Unexposed = Italy)	Bcl-2 oncogene expression and intensity in breast cancer tissue samples	Chi-squared (for Bcl-2 expression) No statistical test (for Bcl-2 intensity)	Bcl-2 expression in Iraqi breast cancer tissue samples was found to be significantly higher ($p = 0.037$) than in Italian samples, and among individuals for which Bcl-2 was positively expressed, Iraqi participants had higher intensities than Italian participants	Not declared
Mryoush & Salim (2015)	Cross-sectional	N/R**	Residents of Baghdad	Participants = 50	Place of residence -	Mitotic index (MI) analysis	No statistical test	The North of Baghdad had the highest mean uranium	Not declared

					Uranium concentration in soil samples (ppm) from five neighborhoods in Baghdad (North - Al-Taji, East - Diyala Bridge, South - Al-Mhmodya, West - Abu Ghraib, Central - Bab-Al-Sharqee)	(number of cells undergoing mitosis/1000 cells in blood sample)		concentration in soil samples (12.90 ppm ± 0.7 SD) and the West had the lowest mean (0.60 ppm ± 0.21 SD), and the mean Mitotic Index in blood samples from the North (2.3 ± 0.059 SD) was higher than the mean MI in samples from the West (0.20 ± 0.3 SD), suggesting a negative correlation	
Neamah & Tawfiq (2015)	Cross-sectional	Jan. 01 – May 31, 2011	Residents of Fallujah	N/R	Place of residence (Exposed = Fallujah, Unexposed = Baghdad)	CBD incidence (number of infants born with CBD per 1000 live births) recorded during a five month period at Fallujah General Hospital (Fallujah) and Yarmouk Teaching Hospital (Baghdad)	Autoregressive model	The coefficient values were found to be higher for Basrah (exposed region) than for Baghdad (unexposed region)	Not declared
Salman (2008)	Ecological: Time trend	1989-2004	Residents of Diyala Governorate	Population based	Time period - Year of cancer diagnosis (Exposed = 2004,	Number of diagnosed cancer cases per year (Baquba	No statistical test	The number of lung cases recorded was higher in 2004 (105 cases) than in 1989 (26 cases), as well as for breast cancer (85 and 17 cases,	Not declared

					Unexposed = 1989)	General Hospital, Primary care center of Baquba and medical centers for cancer treatment in Baghdad)		respectively), and leukemia (92 and 22 cases, respectively) – note: cancer case counts per year do not account for population growth	
Savabieasfa-hani et al (2016)	Case-control	April 2013	Children born with CBDs in Basrah city	Cases = 3 Controls = 6	Uranium and thorium concentrations (ppm) in deciduous teeth, LA-ICP-MS elemental bioimaging	Child with CBD	No statistical test	Uranium and thorium were not detected in any of the samples (detection limit of LA-ICP-MS method was in the ppb range)	Not declared
Shafik (2014)	Case-control	N/R*	Female breast cancer patients in Baghdad	Cases = 41 Controls = 5	Uranium concentrations in 24-hour urine samples ($\mu g \cdot L^{-1}$), KPA-11	Breast cancer (Cases = women with breast cancer living in Baghdad, Controls = healthy women living in Baghdad)	No statistical test	The mean concentration of uranium in urine samples was higher among cases (breast cancer patients, 1.6 $\mu g \cdot L^{-1} \pm$ 0.027 SD) than controls (healthy women, 1.03 $\mu g \cdot L^{-1} \pm$ 0.0202 SD)	Not declared

N/R = Not reported; * Paper suggests after 2003; **Paper suggests after 1991

4.2 Designs, timeframes, locations, and funding

The timeframes of the 31 included human observational studies ranged from 1980-2013 (seven did not report the timeframes of their studies) and the most popular study design employed was case-control, which was used in 55% (n=17) of studies. Other study designs used were cross-sectional (16%, n=5), ecological time trend (26%, n=8), and ecological geographic comparison (3%, n=1). While the populations of concern for all included studies were Iraqi, their specific geographic distribution within Iraq were diverse **(Figure 5).** Eighteen studies (58%) focused on populations at the city or district level (Baghdad, n=6; Fallujah, n=8; Basrah city, n= 3; Ramadi, n=1), nine studies focused on populations at the governorate or province level (Basrah governorate, n=7; Ninawa province, n=1; Diyala governorate, n=1), and four studies focused on populations at the regional level (Southern Iraq). One of the included studies was, in fact, a national household survey (Alborz, 2013). However, that study only used the subset of data collected from Basrah governorate for their analysis of the association between birth defects and warfare contamination.

Publication dates of included studies ranged from 1999-2017, with the majority of articles (77%%) published in the year 2010 or later. Most of the included studies did not declare their sources of funding (55%, n=17). A single study was funded by UNICEF, and one study was funded by the Iraqi Ministry of Higher Education. Six studies were funded by university research grants. Six studies were funded by private NGOs or charitable trusts.

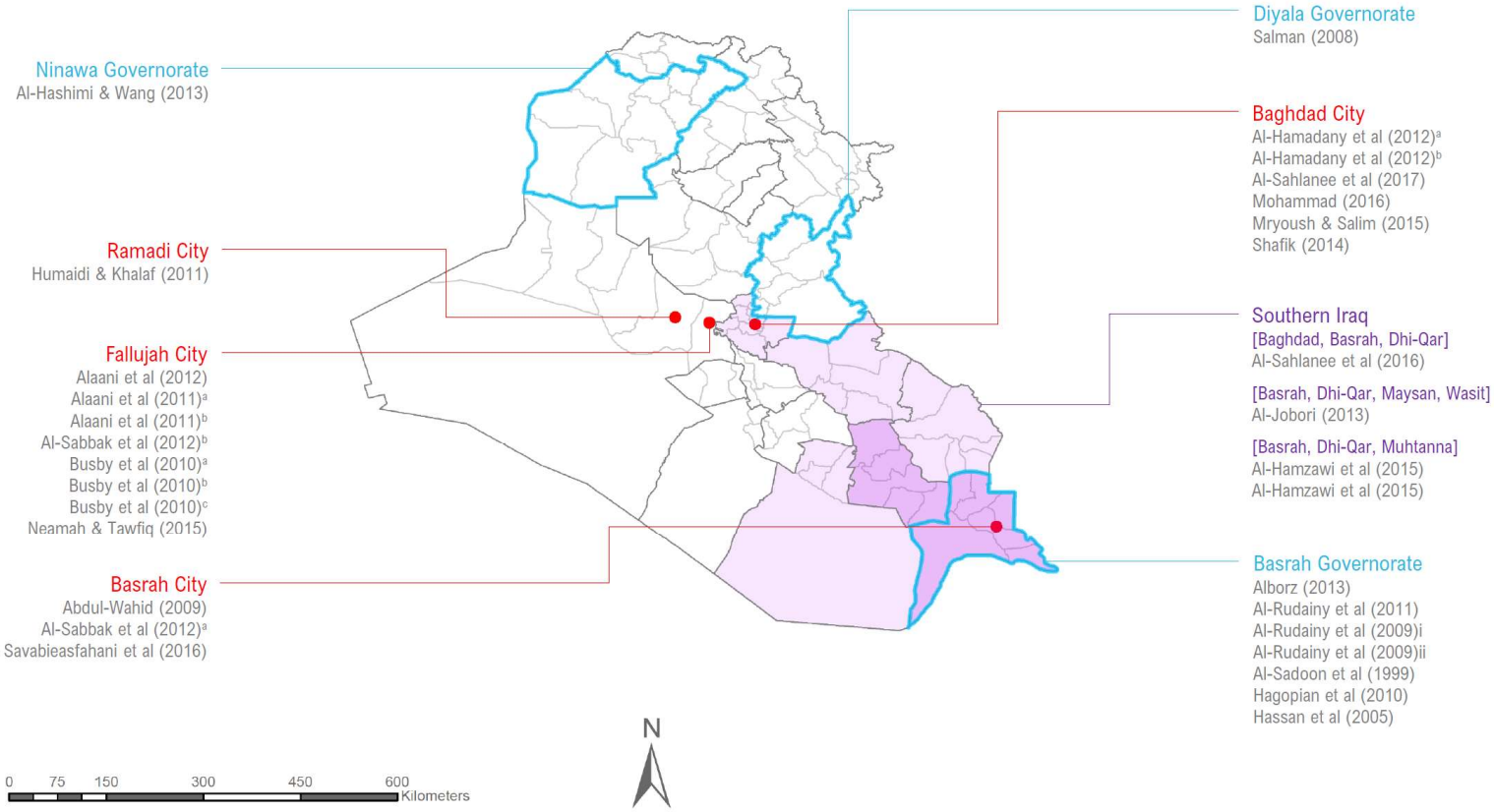

Figure 5. Geographic scope of included studies

4.3 Exposure assessments

4.3.1 Place of residence

Ten studies (32%) used place of residence as a method of comparing exposure to weaponized uranium between populations or study participants. The vast majority of the studies that assessed exposure by place of residence used prior knowledge of locations (within or outside of Iraq) where military attacks by the US or coalition forces involving use of weaponized uranium had or hadn't taken place, or cited literature that documented those locations. Of those studies that assessed exposure by place of residence, only one conducted environmental monitoring to measure uranium concentrations of selected areas (Mryoush & Salim, 2015). One study assessed exposure in place of residence by asking heads of households in a cross-sectional survey if they perceived their household to have been exposed to warfare contaminants (including depleted uranium) (Alborz, 2013).

In comparing exposures between locations, two studies made comparisons *between* cities in Iraq, one of which defined Basrah city as an exposed location (Abdul-Wahid, 2009), and the other which defined Fallujah as an exposed location (Neamah & Tawfiq, 2015). Both defined Baghdad as an unexposed, control location.

The use of Baghdad as a control location should be contrasted with the two studies that compared areas of residence *within* a city in Iraq as a method of exposure assessment. Al-Hamadany et al (2012b) used residence in areas of Baghdad where UNEP had reported detection of depleted uranium as part of their recruitment criteria for participants defined as exposed, and residence outside of those areas as part of their recruitment criteria for participants defined as unexposed. Mryoush & Salim (2015) collected soil samples from

five neighborhoods in Baghdad, and measured the uranium concentrations in those samples using a CR-39 solid state nuclear track detector. While they did not conduct a statistical test of differences in mean uranium concentrations in soil samples between neighborhoods, they reported that the North of Baghdad had the highest mean uranium concentration in soil samples (12.90 ppm ± 0.7 SD), while the West had the lowest mean (0.60 ppm ± 0.21 SD).

Two studies used area of residence within the governorate of Basrah to compare exposure to weaponized uranium. Al-Rudainy et al (2009)[i] conducted a literature review of sources reporting locations contaminated with depleted uranium in the governorate, and assembled those sites in a geographic synthesis, whereas the other study (Alborz, 2013) conducted a survey of households in the governorate and used a questionnaire to ask the head of each household if they believed that their place of residence experienced "warfare contamination" (including weaponized uranium).

Three studies made comparisons between study subjects residing in Iraq (exposed) to study subjects residing in other countries (unexposed). Mohammad (2016) defined residents of Italy as an unexposed population, while Busby et al (2010b), Busby et al (2010c), and Alaani et al (2012) used data from study subjects in Egypt and Kuwait as control populations. Busby et al (2010b) and Alaani et al (2012) each also used a third control population in their analyses (Jordan and UAE, respectively).

4.3.2 Time Period

Nine of the 31 included studies (29%) used historical controls or otherwise used time periods to define exposed and unexposed populations, eight of which used ecological time trend study designs, and one which used a cross-sectional study design. Al-Hashimi &

Wang (2013) defined the years 1980-1990 (prior to the first Persian Gulf War) as an unexposed time period; they defined 1991-2000 (after the first Gulf War, before the US 2003 invasion) and 2001-2010 as exposed time periods, with the most recent period equating with greatest exposure. Likewise, Al-Sadoon et al (1999) defined the year 1990 (prior to the first Gulf War) as an unexposed period, and the years 1991-1998 as an exposed period, with later years equating with greater exposure, and Salman (2008) used year of cancer registration (1989, prior to the first Gulf War, and 2004, following both the first Gulf War and 2003 US invasion) to define exposure groups. Hagopian et al (2010) used year of leukemia registration over the period 1993-2007 as a method of exposure measurement, with more recent years equating with greater exposure, and Hassan et al (2005) used year of registered cancer diagnosis or mortality over a similar period (1997-2002), with more recent years equated with greater exposure. A single cross-sectional study (Busby et al, 2010a) used time period to define exposed and unexposed groups: year of birth prior to 2005 was used to define as an unexposed (or lesser exposed) group, while year of birth after 2005 was used to define as an exposed (or greater exposed) group.

4.3.3 Uranium concentration in human biological samples

Eleven studies (35%) directly measured uranium concentration in human biological samples to assess exposure to weaponized uranium. Of those, four studies measured concentrations in blood samples, three in hair samples, one in urine, one in teeth, and two in other tissues. Notably, only one study examined the isotopic ratio of uranium in Iraqi biological samples. Examining the isotopic ratio of uranium in hair samples collected

from Basrah, Alaani et al (2011) found slightly enriched uranium, not depleted uranium, in their samples.

4.3.3.1 Uranium concentrations in blood

All four studies that measured uranium concentration in blood samples used CR-39 solid state nuclear (fission) track detectors. The highest mean uranium blood concentration reported among the four studies was 950 ppb ± 620 SD, measured in blood samples of women (n=50) who gave birth in Baghdad (time period of sample collection and analysis were not reported) (Al-Sahlanee et al, 2017). In a separate study published by the same authors one year prior, the mean uranium blood concentration measured among women (n=47) who gave birth to dead or deformed infants in Baghdad was reportedly 1.90 ppb ± 0.19 SD (Al-Sahlanee et al, 2016). Al-Hamadany et al (2012a) found the mean uranium concentration in blood samples of healthy individuals (n=14) living in uncontaminated areas of Baghdad (neighborhoods where depleted uranium weapons had reportedly not been used) to be 110 ppb ± 9 SE. Outside of Baghdad, Al-Hamazawi et al (2014) found the mean uranium concentration in blood samples of leukemia patients from the governorates of Basrah, Muthanna, and Dhi-Qar (n=30) to be 2.87 ppb ± 0.11 SD, compared to 1.43 ppb ± 0.07 SD among healthy individuals from the same areas (n=30).

4.3.3.2 Uranium concentrations in hair

In contrast to the studies that used CR-39 fission track detectors to determine uranium concentrations in blood, the three studies that assessed uranium concentrations in

hair samples used inductively coupled mass spectrometry instruments (ICP-MS). All three of the hair studies recruited participants from the city of Fallujah. In scalp hair samples (n=25) collected from parents (mothers and fathers) of children with congenital birth defects, Alaani et al (2011a)found a mean uranium concentration of 0.16mg·kg^{-1} ± 0.11 SD. In a separate study of long hair samples (n=4) from a subset of the same mothers, Alaani et al (2011b) found a slightly higher mean uranium concentration of 0.26 U mg·kg^{-1} ± 0.09 SD. Among parents (mothers and fathers) of children with birth defects (n=103), Al-Sabbak et al (2012b) found a mean uranium concentration of approximately 0.09 mg·kg^{-1} ± 0.05 SD (findings were reported in a figure only, not in a table or text).

4.3.3.3 Uranium concentrations in urine, teeth, and other tissues

Using a kinetic phosphorescence analyzer (KPA-ll), Shafik (2014) found a mean uranium concentration of 1.6 µg·L^{-1} ± 0.027 SD in urine samples collected from female breast cancer patients in Baghdad (n=41). Looking at tissues samples from Southern Iraqi cancer patients and healthy controls, Al-Hamzawi et al (2015) and Al-Jobori et al (2013) both used CR-39 fission track detectors to measure uranium concentrations. Al-Jobori et al (2013) reported a maximum uranium concentration of 1940 ppb in lung tissue from a 53 year old male Iraqi soldier in Basrah (no mean concentration reported in the study), and of the four tissue types tested by Al-Hamzawi et al (2015) (kidney, breast, stomach, and uterus), they found the highest mean uranium concentration in cancerous kidney tissues (6.51 µg·kg-1 ± 0.20 SD). Savabieasfahani (2016) did not detect any uranium in a small

sample (n=3) of deciduous tooth samples collected from children with congenital birth defects in Basrah, via the use of laser ablation ICP-MS elemental bioimaging.

4.3.4 Other methods of uranium exposure assessment

Finally, a single study (Humaidi & Khalaf, 2011) defined exposure to weaponized uranium by source of bullet wounds among gunshot patients in Ramadi. Patients who had been shot by US or coalition forces were defined as exposed, while patients who had gunshot wounds from sources other than US or coalition forces, were defined as unexposed.

4.4 Health outcomes of interest

With regard to health outcomes, 10 of the 31 included studies selected congenital birth defects as their outcome of interest (32%). Other birth-related outcomes among included studies were: anthropometric measurements of newborns (one study), birth-sex ratio (one study), and infant mortality rate (one study). Additionally, twelve studies selected cancer as their outcome of interest (39%), and a single study selected the expression of the oncogene BCL-2 (an important prognosis indicator for breast cancer) as the outcome of interest. Three studies (10%) measured outcomes related to immune system function, and two included studies (6%) (case-control study designs) selected cases based on multiple outcomes – they defined cases as cancer patients, or parents of children born with congenital birth defects – and grouped both outcomes together in their analysis.

4.5 Risk of bias assessment for individual studies

Risk of bias determinations were made across eight methodological domains for all 31 included studies. We concluded that there was generally a high risk of bias across the body of evidence **(Figure 6A).** Using the Navigation Guide's risk of bias tool (Johnson et al, 2014), we found that confounding was the domain with the highest risk of bias, followed by blinding, and other sources of bias **(Figure 6B).** Justifications for risk of bias determinations for each included study are provided in **Appendix 7.** With the exception of two studies, all of our included studies were judged to be high risk of bias, or probably high risk of bias, in at least one domain.

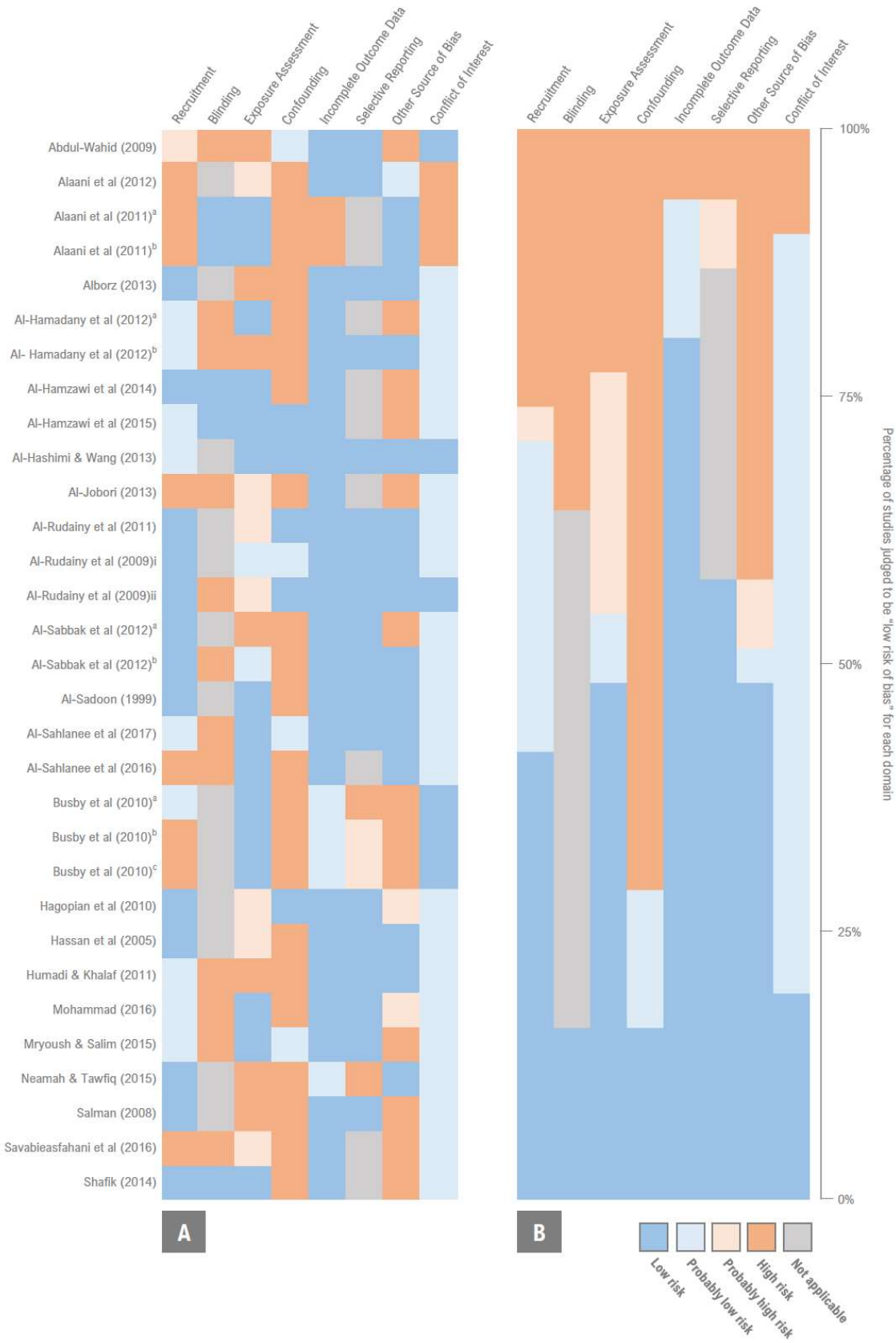

Figure 6. (a) Risk of bias assessments for individual studies, and (b) across studies

4.6 Effect of exposure by outcome

4.6.1 CBD Incidence

Ten studies selected congenital birth defects as their health outcome of interest. Of those, four reported CBD incidence in their target population in Iraq (two studies in Fallujah city, one in Basrah city, and one in Basrah governorate), and then compared CBD incidences between exposed and unexposed populations geographically or temporally.

In Fallujah, Alaani et al (2012) found a CBD incidence of approximately 144 per 1000 live births over an 11-month period in 2010. Because the authors used a hospital surveillance study design, the number of CBD cases was known exactly, but the total number of live births was estimated. The CBD cases in the study were diagnosed in one of three pediatric clinics which recieved approximately one third of all births at Fallujah General Hospital. Therefore, the number of CBD cases was divided by one-third of the total number of live births registered at the hospital over the study period in order to calculate CBD incidence. The authors then compared their findings from Fallujah to CBD incidences in Egypt (31.7 per 1000 live births), Kuwait (12.5 per 1000 live births), and the UAE (7.9 per 1000 live births), and found that the CBD incidence in Fallujah was many times higher than the incidences reported in unexposed populations in the Arab region.

Neamah & Tawfiq (2015) also used a hospital surveillance study design to compare CBD incidence at Fallujah General Hospital (defined as the exposed population) over a five month period in 2011 to CBD incidence at Al-Yarmouk Teaching Hospital in Baghdad (defined as the unexposed population) during the same period. They found the CBD incidence in the exposed population (Fallujah) to be significantly higher than in the

unexposed population (Baghdad). However, the study reported only the outcome of the statistical analysis, not the measured incidences either hospital.

In an earlier study from Basrah, Al-Sadoon et al (1999) recorded the total number of infants born with CBDs and total number of live births at "the main children and maternity hospital in Basrah" (the name of the hospital was not reported) from 1990-1998. They found that for the period 1991-1994 that the CBD incidence was 2.5 per 1000 live births, compared to the period 1995-1998 for which the CBD incidence was 4.57 per 1000 live births. The difference between the two periods was statistically significant (SND test, $p<0.01$).

Using birth records from Al Basrah Maternity Hospital, Al-Sabbak et al (2012a) found that CBD incidence increased by 17 times in less than a decade – from 1.37 per 1000 live births in 1994, to 23 per 1000 live births in 2003. They also found that some specific types of birth defects were more prevalent in Basrah than reported in other countries. For example, the incidence of hydrocephalus in Al Basrah in 2003 (3 per 1000 live births) was found to be three times the world average (1 per 1000 live births) and five times the incidence reported in the United States (0.6 per 1000 live births).

4.6.2 CBD and uranium exposure case-control studies

The remaining six included studies that selected birth defects as their outcome of interest used case-control study designs to compare uranium exposure between selected cases (children born with CBD) and controls (non-CBD). Five of those studies directly measured uranium concentrations in human biological samples, while one assessed self-

reported exposure to war contaminants in a household questionnaire (Alborz, 2013). Three of the studies were carried out with participants from Fallujah city, two with participants from Basrah governorate, and one with participants from Southern Iraq (Dhi-Qar and Basrah) and Baghdad.

Alaani et al (2011a) found a mean uranium concentration of 0.16 ppm (SD 0.11) in scalp hair samples collected from parents (n=25) that gave birth to children with CBDs at Fallujah General Hospital between 2009-2010. They also found that uranium concentrations were higher in hair samples collected from mothers than fathers, but they did not test the difference for statistical significance. A control population in Southern Israel was reported to have a mean uranium concentration in hair samples of 0.062 U mg·kg-1, which was found to be significantly lower than the exposed population in Fallujah (p=0.016).

In long hair samples from four mothers in the same cohort plus two new mothers that did not participate in first scalp hair study (for a total sample size of n=6), Alaani et al (2011b) found a mean uranium concentration of 0.27 ppm in hair samples taken 6-8cm from the scalp, and a lower mean of 0.23 ppm in hair sample taken 24-31cm from the scalp. Compared to a control population in Sweden, uranium concentrations analyzed by distance from scalp did not decrease as steeply in the samples collected from Fallujah. The study argued that this was indicative of higher uranium exposure in the past among the Fallujah participants.

In the third case-control study from Fallujah, Al-Sabbak et al (2012b) found a mean uranium concentration of approximately 0.09 mg·kg-1 ± 0.05 SD in hair samples collected from parents who gave birth to children with CBDs between May and August

2010 (n=103). The mean uranium concentration in hair samples collected from parents who gave birth to normal infants in Fallujah (n=9) was found to be approximately 0.07 mg·kg-1 ± 0.05 SD. However, the difference in means was not tested statistically, and the findings were reported in a figure only, not in a table or text.

Of the two birth defect case-control studies from Basrah, one measured uranium concentration in deciduous teeth from children (n=3) collected in April 2013, and the other used a household survey (conducted in 2010) to assess participants' self-reported exposure to war contaminants. In the study of deciduous teeth, uranium was not detected in any of the tooth samples collected from cases or controls (Savabieasfahani et al, 2016). In the household survey, a significantly higher proportion of children with CBDs were found to reside in households that reported exposure to war contaminants, compared to those that did not (Alborz, 2013).

In the remaining birth defect case-control study, Al-Sahalanee et al (2016) measured uranium concentrations in maternal blood and umbilical cord samples from infants born dead or with congenital birth defects, compared to normal infants, in Southern Iraq. The mean uranium concentration in blood collected from mothers who gave birth to dead or deformed infants (n=47) was 2.43 ppb ± 0.89 SD, which was significantly higher than the mean uranium concentration in blood collected from to mothers who gave birth to normal and alive infants (n=53, 1.26 ppb ± 0.51 SD) ($p < 0.05$). in umbilical blood, the mean uranium concentration for dead and deformed infants (n=47) was 1.99 ppb ± 0.78 SD, which was significantly higher than the mean concentration for normal and alive infants (n=53, 0.97 ppb ± 0.38 SD) ($p < 0.05$).

4.6.3 Other Birth Outcomes

Three studies selected birth outcomes other than congenital birth defects as their outcomes of interest.

Al-Sahalanee et al (2017) carried out a cross-sectional study at a hospital in Baghdad to measure association between uranium exposure and anthropometric measurements of infants. The study used a CR-39 fission track detector to measure uranium concentration in maternal and umbilical blood samples in 50 mother-infant volunteer pairs recruited from a hospital in Baghdad. The study found that uranium concentrations in both maternal and umbilical cord blood samples were negatively correlated with measurements for body length, birth weight, and head circumference. All associations were statistically significant ($p < 0.05$) except for the association between uranium concentration in umbilical cord samples and infant body length.

Busby et al (2010a) examined birth-sex ratio in Fallujah using a cross-sectional household survey. They found that the sex ratio of boys to girls for children born during the period 2006-2010 was 0.86, compared to 1.182 for children born between 2001-2005, 1.109 for children born between 1996-2000, and 1.010 for children born between 1991-1995. The birth-sex ratio for children born between 2006-2010 was found to differ significantly from the expected ratio ($p < 0.01$).

In the same household survey, Busby et al (2010b) also investigated the infant mortality rate (IMR) in Fallujah between 2006-2010. They found the IMR in Fallujah over that time period to be 80 per 1000 births, which was four times higher than the IMR reported in Egypt and Jordan ($p < 0.00001$), and nine times higher than the IMR in Kuwait (p-value not reported).

4.6.4 Cancer incidence

Twelve studies selected cancer or cancer mortality as their outcome of interest. Of those, seven reported cancer incidence or cancer mortality rate in their target population in Iraq (five studies in Basrah governorate, one in Ninawa province, and one in Fallujah), and then compared cancer incidences or mortality rates between exposed and unexposed populations geographically or temporally.

In Basrah governorate (Southern Iraq), Al-Rudainy et al (2011) conducted an ecological time-trend study to determine whether the incidence of childhood Leukemia (0-14 years of age) had changed over the time period 2004-2009. They defined 2004 as the least exposed time period, and 2009 as the greatest exposed time period. In 2004, the rate of childhood Leukemia was 2.70 per 100,000 population, and in 2009, the rate was 3.10, but the rate also varied between 2.85 and 4.49 in the intervening years. Although the case-counts of childhood leukemia increased over the study period, the rate of childhood Leukemia per 100,000 population was found to have decreased by 0.123 between 2004-2009. The test for trend was not significant (p=0.81).

In an second (earlier) study by the same authors, Al-Rudainy et al (2009)ii conducted another ecological time-trend study of childhood leukemia in Basrah governorate, but over the time period 2003-2007. They defined 2003 as the least exposed time period, and 2007 as the greatest exposed time period. In 2003, the incidence of childhood leukemia (1-14 years of age) in Basrah was 4.25 per 100,000 population, and in 2007 the incidence was 3.80 per 100,000 population. Over the 5 years study period, no increase in childhood leukemia incidence was observed, but the authors performed no statistical test for trend.

The same authors, Al-Rudainy et al (2009)i, conducted a third study investigating cancer incidence in Basrah governorate – this time, an ecological geographic comparison. This study compared cancer incidence in 2006 between districts in Basrah governorate. Districts were categorized as unexposed, low exposure, or high exposure, based on a literature review and geographic collation of DU-impacted sites in the governorate. In unexposed districts, the reported cancer incidence in 2006 was approximately 62 per 100,000 population, in low exposure districts it was approximately 58 per 100,000, and in high exposure districts it was approximately 65 per 100,000. Incidences between exposed and unexposed districts were reported in a figure only, not in a table or text. The study concluded that there was no statistical correlation between level of DU contamination and cancer incidence by district in Basrah in 2006 ($r= -0.01$, $p= 0.98$).

Hagopian et al (2010) conducted an ecological time-trend study of childhood leukemia incidence over a longer period (1993-2007) in the Basrah governorate. Childhood leukemia incidence was determined for three year interval and tested for trend using standard linear regression. The study found that for the period 1993-1995, the incidence of childhood Leukemia in Basrah was 3.03 per 100,000 population, and for the period 2005-2007 it was 8.4 per 100,000. The statistical test revealed a significant ($p=0.03$) trend of increasing incidence of childhood leukemia in Basrah between 1993-2007.

Hassan et al (2005) conducted an ecological time-trend study of cancer incidence (for all registered types and age groups) and cancer mortality rate over the period 1997-2002 in Basrah governorate. They defined 1997 as the least exposed period, and 2002 and greatest exposed period. The study found that cancer incidence decreased from 33.9 per 100,000 population in 1997, to 31.8 per 100,000 population in 2002, whereas the cancer

mortality rate increased from 17.9 per 100,000 population in 1997, to 25.4 per 100,000 population in 2002. The study did not report a statistical test for trend, but concluded that no significant increases in cancer incidence or mortality rate were observed in Basrah over the study period.

In Ninawa province (Northern Iraq), Al-Hashimi & Wang (2013) conducted an ecological time-trend study of cancer incidence rate ratio (IRR) over the period 1980-2010. In 1980, the incidence for all cancer types was found to be 23.9 per 100,000 population in Ninawa province, and in 2010 it was 45 per 100,000 population. Cancer IRR was determined for 10-year periods, and differences in IRR between periods was investigated using Poisson regression analysis. The study found that IRR for most cancer types in Ninawa significantly decreased in the second (1991-2000) and third period (2001-2010) compared to the first period (1980-1990) ($p < 0.01$).

In the city of Fallujah (central Iraq), Busby et al (2010c) calculated the relative risk for cancer incidence between Fallujah (exposed population) and Egypt (unexposed population). Using a household survey in Fallujah, the study determined that the cancer incidence among their study population was 62 per 100,000 over the period 2005-2010. The Relative Risk (RR) for cancer incidence in Fallujah between 2005-2010 compared to Egypt (1999) was 4.22 (CI: 2.8 - 6.6, $p < 0.00000001$).

4.6.5 Cancer case counts

A single study selected cancer case counts as its outcome of interest (Salman, 2008). Using an ecological time-trend study design, the study compared number of

diagnosed case counts per year over the time period 1989-2004 in the Diyala governorate and found that the number of lung cases recorded was higher in 2004 (105 cases) than in 1989 (26 cases), as well as for breast cancer (85 and 17 cases, respectively), and leukemia (92 and 22 cases, respectively).

4.6.6 Cancer and uranium exposure case-control studies

Four included studies that selected cancer as their outcome of interest used case-control study designs to compare uranium exposure between selected cases (patients with cancers) and controls (healthy patients, or patients with benign tumors). All four studies directly measured uranium concentrations in human biological samples. Two of the studies were carried out with participants from the Southern Iraqi Governorates of Basrah, Muthanna, and Dhi-Qar (Al-Hamzawi et al, 2015; Al-Hamzawi et al, 2014). One study was carried out with participants from five Southern Iraqi governorates (Basrah, Muthanna, Dhi-Qar, Maysan, and Wasit) (Al-Jobori, 2013), and one study was carried out with participants from Baghdad (Shafik, 2014).

Al-Hamzawi et al (2015) recruited patients with cancers of the kidney (n=6), breast (n=6), stomach (n=6), and uterus (n=6) for a total 24 cases, and 12 healthy control volunteers, from Southern Iraq. Using a CR-39 fission track detector, they measured uranium concentration in cancerous tissues and corresponding tissues from healthy volunteers. Significant differences in mean uranium concentrations were found between tissues from cancer patients compared to healthy controls for all cancer types. The mean uranium concentration in kidney tissues from cancer patients was 6.51 μg·kg-1 ± 0.20 SD,

comparted to 4.11 μg·kg-1 ± 0.38 SD in healthy volunteers ($p < 0.001$). The mean uranium concentration in breast tissues from cancer patients was 5.04 μg·kg-1 ± 0.27 SD, comparted to 2.96 μg·kg-1 ± 0.16 SD in healthy volunteers ($p < 0.01$). The mean uranium concentration in stomach tissues from cancer patients was 5.22 μg·kg-1 ± 0.22 SD, comparted to 3.11 μg·kg-1 ± 0.29 SD in healthy volunteers ($p < 0.01$). The mean uranium concentration in uterus tissues from cancer patients was 4.61 μg·kg-1 ± 0.32 SD, comparted to 2.28 μg·kg-1 ± 0.51 SD in healthy volunteers ($p < 0.01$).

The same authors (Al-Hamzawi et al, 2014) conducted an earlier case-control study with blood samples collected from Leukemia patients from Southern Iraq (n=30) and healthy volunteers from the same area (n=30). The study assessed uranium concentration in blood samples using a CR-39 fission track detector and found that the mean uranium concentration among sample from leukemia patients (cases) to be 2.87 ppb ± 0.11 SD, which was significantly higher than the mean concentration in samples from healthy volunteers (1.43 ppb ± 0.07 SD) ($p<0.001$). The study also found that mean uranium concentrations in samples from Basrah governorate (both cases and controls) was higher than the mean concentration in blood samples from the other governorates in Southern Iraq (Muthanna and Dhi-Qar) ($p<0.05$).

Al-Jobori et al (2013) also used a CR-39 track detector to measure uranium concentration in tissue samples from cancer patients (n=9) and health controls in Southern Iraq (n=3). The authors did not report a mean uranium concentration in tissues samples collected from cancer patients, but the maximum concentration reported was 1940 ppb in a lung tissue sample collected from a 53 year old male Iraqi soldier. The study reported that they did not detect uranium in any tissues collected from healthy controls.

Shafik (2014) used a kinetic phosphorescence analyzer (KPA-11) to measure uranium concentrations in 24-hour urine samples collected from female breast cancer patients (n=41) and healthy female volunteers (n=5) in Baghdad. The study found that the mean concentration of uranium in urine samples was higher among breast cancer patients (1.6 μg·L-1 ± 0.027 SD) than controls (healthy women, 1.03 μg·L-1 ± 0.0202 SD), but the difference in means was not tested statistically.

4.6.7 Mixed outcome case-control studies

Two included studies (with the same set of participants, published in the same article) used case-control study designs and selected cases based on multiple outcomes – they defined cases as cancer patients, or parents of children born with congenital birth defects – in Baghdad.

The stated objective of the study by Al-Hamadany et al (2012a) was to compare uranium concentration in blood samples collected from cases and (healthy) controls. The study recruited participants from Baghdad in five categories: cancer patients prior to treatment (n=15), cancer patients currently receiving treatment (n=15), women who had given birth to children with congenital birth defects (n=15), volunteers who were occupationally exposed to ionizing radiation (n=14), residents of areas of Baghdad that were reportedly contaminated with DU (n=15), and healthy volunteers residing in areas of Baghdad not reported to be contaminated with DU (n=14). In the study's findings, it reported the mean uranium concentration measured in blood samples collected from the healthy unexposed group (n=14), and the mean uranium concentration in blood samples

from participants from all other groups (n=74). The study found that mean uranium concentrations from the control population (0.11ppm ± 0.009 SE), was significantly lower than the mean uranium concentration in samples from participants from all other recruitment groups (0.21 ppm ± 0.01 SE) ($p<0.05$).

The second study Al-Hamadany et al (2012b) assessed variables related to immune system function, but also used health outcomes in its definition of exposed cases. Cancer patients, and mothers of children with birth defects, were defined as exposed, as were individually occupationally exposed to ionizing radiation in a medical setting, and individuals residing in areas of Baghdad that were reportedly contaminated with DU. Controls were defined as healthy individuals living in uncontaminated areas of Baghdad. The study found that white blood cell counts were significantly higher among participants defined as exposed, and hemoglobin concentrations were significantly lower, compared to the group defined as unexposed ($p<0.05$).

4.6.8 BCL-2 expression and intensity

One case-control study examined the expression and intensity of the oncogene BCL-2, an important prognostic factor for breast cancer, in Iraqi breast cancer patients (n=50) and compared findings to a control population in Italy (n=30) (Mohammad, 2016). The study found that BCL-2 expression in Iraqi breast cancer tissue samples was found to be significantly higher ($p = 0.037$) than in Italian samples, and among individuals for which BCL-2 was positively expressed, Iraqi participants had higher intensities than Italian participants.

4.6.9 Immune system function

Three of our included studies selected immune system function as their outcome of interest. Abdul-Wahid (2009) compared the percentage of white blood cells in blood samples recruited from participants in Basrah (exposed population, n=50) and 50 aged-matched volunteers from Baghdad (unexposed population). The study found that cases had lower levels of selected lymphocytes (CD3, CD4, CD8, CD19, and CD56) compared to controls (p-values were not reported).

Humaidi & Khalaf (2016) investigated 10 variables (W.B.C. count, hemoglobin concentration, erythrocyte sedimentation ratio, total serum Bilirubin, alkaline phosphates enzyme concentration, serum transferees enzymes concentration, serum Creatinine concentration, blood urea concentration, mitotic index) related to immune system function in patients with bullet wound injuries in Ramadi. They compared their findings for each variable between patients who had been shot by the US military or coalition forces (n=196), to patients who had gunshot wounds from other sources (n=19), with the assumption that bullets from the US military contained DU. The study found that there were significant differences ($p<0.05$) between cases and controls for all outcomes measured.

Mryoush & Salim (2015) assessed the Mitotic Index in blood samples collected from residents of Baghdad (n=50) living in five areas of Baghdad where the study authors measured elevated levels of uranium in soil samples. The study found that their selected area in the north of Baghdad had the highest mean uranium concentration in soil samples

(12.90 ppm ± 0.7 SD) and the west had the lowest mean (0.60 ppm ± 0.21 SD). The mean Mitotic Index in blood samples from the North (2.3 ± 0.059 SD) was higher than the mean MI in samples from the West (0.20 ± 0.3 SD). The authors suggested that their findings indicated a negative correlation between uranium exposure and percentage of cells undergoing mitosis. Conversely, this finding could be stated as a positive associate between uranium exposure and adverse health effects. However, the authors conducted no statistical test of association.

CHAPTER V

DISCUSSION

"Iraq is an epidemiological nightmare."

- An expert on depleted uranium at the Vienna-based International Atomic Energy Agency[1]

5.1 Critical appraisals of study findings by outcome

5.1.1 CBD incidence

The CBD incidence studies in Fallujah and Basrah unanimously found higher incidences among exposed populations compared to unexposed populations (geographically or temporally). However, in interpreting these results, two questions arise: First, are the differences in incidence real or artificial? In other words, are they due to differences in surveillance, detection, registration, or sampling methods, or true differences in the populations? Second, if the differences are real, is uranium exposure a primary causal factor, or can the differences be explained by other causal factors (confounders)?

Are the observed differences in CBD incidence real?

In their review of birth defect studies in Iraq, Al-Hadithi et al (2012) suggested that findings of increased CBD incidence in Basrah are artificial; the review argued that public fear about depleted uranium exposure in Iraq could have led to over reporting of CBD incidence in recent (post-war) time periods, thus leading to invalid results. However, all of the CBD incidence studies included in this systematic review used prospective

[1] As reported by Allison Abbott in *Nature*, September, 2001

hospital surveillance or retrospective hospital registry data to determine the total number of cases and live births among their target populations. A major strength of such methods (hospital surveillance and registry data acquisition) is that they are not subject to recall bias or over reporting. This makes them a more reliable method for measuring CBD incidence than cross-sectional surveys or questionnaires. All CBD cases in our included studies were diagnosed by medical doctors and reported to official hospital registries. According to Al-Hadithi et al (2012), hospital registries in Basrah are "poor and inefficient". If this is true, it could only lead to an underreporting of total cases in contemporary time periods, not overreporting.

Despite the methodological strengths of hospital surveillance and registry studies for determining CBD incidence, they have two potential limitations.

First, differences in technology and healthcare systems (geographically or temporally) could lead to differences in CBD detection, leading to the false impression that CBD incidences are different between populations. Typically, CBD incidence is highest in developed countries, where detection and surveillance is most sensitive (Boyle and Cordero 2005). In the study by Alaani et al (2012), CBD incidence in Fallujah in 2010 was compared to CBD incidences reported in Egypt, Kuwait, and the UAE in 1998, 2005, and 1995, respectively. Because there is no assurance that surveillance and registration methods were the same in those countries at different time periods, the observed differences in CBD incidence between Fallujah and other Arab countries may be artificial.

Second, a short study period (less than two years), could give an unrepresentative detection rate of rare and sporadic CBDs (Al-Hadithi et al, 2012). Only one of the CBD incidence studies included in this systematic review used time periods of longer than 2-

years to assess CBD incidence for both case and control populations (Al-Sadoon et al, 1999). Alaani et al (2012) used a study period eleven months, while Neamah & Tawfiq (2015) used a time period of five months. Al-Sabbak et al (2012)a, used data from a single year (1994) to calculate CBD incidence for their comparator population, but data from a 9-year period (2003-2011) for their exposed population.

Taking these points into consideration, we can say that the differences in CBD incidence observed by Al-Sadoon et al (1999) in Basrah is probably true, but the differences in CBD incidence found among the other studies are at high risk of bias.

Is uranium exposure the primary causal factor in observed differences?

After considering whether the observed differences in CBD incidence are true, we should consider whether the observed differences are due to uranium exposure, or to other confounding variables. There are many known factors associated with CBD incidence. Among them are consanguinity (Tadmouri, Nair et al. 2009) and maternal malnutrition (folate deficiency) (Czeizel, Dudás et al. 2013). Exposure to other environmental contaminants, like lead from the use of leaded gasoline or bacteria from damaged sewage infrastructure, could also be associated with increased CBD incidence (Boyle and Cordero 2005). In Iraq, it is well-documented that these exposures and confounding variables also increased after the first and second gulf wars.

None of the four CBD incidence studies collected data on possible confounders for both their exposed and control populations. One of the two Fallujah studies found that consanguinity among parents (defined as marriage to first, second, or third cousins) was present in 162 (56.8%) of the observed CBD cases, but the study did not assess the rate of consanguinity among parents who gave birth to infants without CBD (Alaani et al, 2012).

Without controlling for confounders, it is not possible to conclude that observed differences in CBD incidence are attributable to uranium exposure.

5.1.2 CBD and uranium exposure case-control studies

Of the six CBD studies that compared uranium exposure between cases and controls, five found a positive association between uranium exposure and CBD outcomes. The one exception was Savabieasfahani et al (2016), which did not detect any uranium in tooth samples from cases or controls, despite the authors' expectations.

The average adult total body burden for uranium globally is 56 ppb (Bleise, Danesi et al. 2003). In a sample of healthy participants from Slovenia without occupational exposure to uranium (i.e. only natural background exposure), the median concentration of uranium in hair was found to be 11.5 ppb (Byrne and Benedik 1991), compared to 160 ppb found in the scalp hair samples from parents who gave birth to children with birth defects in Fallujah by Alaani et al (2011)a and 90 ppb found by Al-Sabbak et al (2012)b, suggesting greater uranium exposure among the Iraqi population. In contrast, the average uranium concentration in blood globally is 2 ppb (Bleise, Danesi et al. 2003). The mean uranium concentration detected in blood of mothers gave birth to dead or deformed infants in Southern Iraq by Al-Sahalanee et al (2016) was 2.43 ppb ± 0.89 SD, which is approximately the same as the expected background concentration.

For most of these studies, the method of uranium exposure assessment was robust. Five of the six studies used reliable laboratory techniques (CR-39 fission track detectors or ICP-MS) to measure uranium concentrations in biological samples collected directly from

cases. Although the methods for measuring uranium concentrations were robust, they were not without limitations. Uranium introduced to the environment through the use of conventional weapons by the US or other militaries is not the only source of uranium exposure faced by the Iraqi population. The use of phosphate fertilizers can increase exposure to natural uranium (and thus lead to increased uranium concentrations in human biological samples), as well as occupational exposure in fertilizer plants or phosphate and uranium mines (Brugge and Oldmixon 2005).

Only one study measured the isotopic ratio of uranium in samples in order to determine whether the source of uranium was natural or artificial, and found that the uranium detected in hair samples from participants in Fallujah had an enriched, rather than depleted, isotopic signature. While this finding suggests that the source of uranium in participants was not natural, it is questionable whether or not the uranium was derived from conventional weapons used by the US or coalition forces. One possible source of non-natural uranium exposure in Iraq is the Al-Tuwaitha nuclear power plant, which was bombed and looted during the 2003 invasion (Chesser, Rodgers et al. 2009). Hundreds of barrels of uranium oxide went missing from the plant after it was destroyed, and only a fraction of the barrels were recovered. In some instances, empty (but still radiologically contaminated) barrels were found in nearby towns, and were being used as food and water storage containers (Chesser, Rodgers et al. 2009).

Additionally, lack of blinding of key personnel is an important element of the study design, particularly in the use of CR-39 track detectors, that can introduce bias into study results. To measure uranium concentration using a CR-39 fission track detector, track marks on a plastic polymer product must be visually counted by a lab technician (Nejad,

Hasani et al. 2014). It is a manual, not automated, process, and thus bias is capable of being introduced when the counting technician is not blinded to whether samples come from cases or controls (Nejad, Hasani et al. 2014). Only one CBD case-control study used a CR-39 track detector, and it did not report that their samples were recoded or that lab technicians were otherwise blinded (Al-Sahalanee et al, 2016). Two of the five laboratory studies reported that their samples were recoded, and those studies used ICP-MS to measure uranium concentrations, not CR-39 track detectors (Alaani et al, 2011a; Alaani et al 2011b).

Furthermore, there are a few important confounding variables which affect uranium concentration in human biological samples – namely, age and sex. Uranium concentration in bone and other storage sites in the body increases with age (Kurttio, Harmoinen et al. 2006, Larivière, Packer et al. 2007), and thus an older age cohort would be expected to have a higher mean uranium concentration in selected biological samples than a younger age cohort. Additionally, some studies have found that adult women have a greater total body burden of uranium than adult men (Kurttio, Komulainen et al. 2005, Alaani 2011). Because tobacco is fertilized with phosphate fertilizers, and because smoking can damage kidney function, uranium concentration has been found to be higher in smokers than in non-smokers (Brugge and Oldmixon 2005). None of the five laboratory studies accounted for the confounders of age, sex, or tobacco use in their analyses.

5.1.3 Other Birth Outcomes

The same possible sources of methodological bias present in the CBD and uranium exposure case-control studies occur in the cross-sectional study by Al-Sahalanee et al (2017). The isotopic ratio of uranium detected in maternal and umbilical cord samples was not examined, and the study cannot be said to strictly measure uranium derived conventional uranium weapons used by the US or coalition forces. While the study did collect data on tobacco use and age of study participants, it did not account for those confounders in its tests for association.

The conclusion reached by Busby et al (2010)a regarding birth-sex ratio in Fallujah does not seem well-founded, given the lack of control for confounding variables, as well as the selective reporting of the study's outcomes. Birth-sex ratio has been found to be affected by maternal nutritional status; specifically, low-calorie maternal diets have been found to be associated to higher female to male birth sex ratios (Mathews, Johnson et al. 2008). During the sieges of Fallujah in 2004, the import of food into the city of Fallujah was interrupted (Ismael and Ismael 2005), so it is reasonable to expect that maternal caloric intake would have been restricted during that period and may be a possible confounder in the study. Additionally, the study did not report the birth-sex ratio for age cohorts above 19 years. The next age cohort (20-24 years, children born between 1986-1990) has a birth-sex ratio even lower than the 0-4 years age cohort (which represents children born between 2006-2010); the study data shows a birth-sex ratio of 776 males per 1000 females in the 20-24 year cohort (although the ratio was not calculated or explicitly reported in the study) compared to 860 males per 1000 females in the 0-4 year age cohort (which *was* calculated and explicitly reported).

In the infant mortality study by Busby et al (2010)b, the IMR in Fallujah was compared to the IMRs in other Arab countries. The study does not cite where, when, or how the infant mortality data for the control populations (Egypt, Jordan, and Kuwait) were obtained, putting the study at high risk for recruitment bias. Infant mortality rates have also been shown to be associated with a large number of social-ecological factors including environmental exposures, maternal malnutrition, poverty, and poorly functioning health care systems (ZAKIR and WUNNAVA 1999, Muldoon, Galway et al. 2011). These factors almost certainly differed between Fallujah and the control populations in Egypt, Jordan, and Kuwait, and were not accounted for in the study's analysis.

5.1.4 Cancer incidence

Of the five studies that investigated cancer incidence in Basrah governorate only one study found that cancer incidence among their exposed population differed significantly from their (temporal or geographic) control populations. The remaining Basrah cancer incidence studies found no significant differences over time, or between exposed and unexposed districts in the governorate. A possible explanation for why the study by Hagopian et al (2010) found a significant increase, while the other studies did not, is that Hagopian et al (2010) used a longer time frame for analysis, making it the most rigorous of the five studies. There is a high certainty that the findings by Hagopian et al (2010) regarding cancer incidence reflect real changes in the population. However, the method of exposure assessment by Hagopian et al (2010) is indirect, as they explicitly state in their publication. Childhood leukemia is known to be associated with exposure to ionizing radiation, as well as benzene and some cytotoxics (Eden 2010). In addition to DU

contamination, Basrah was impacted by smoke from oil well fires during the first Gulf War, leading to greater exposure to the Leukemogen benzene among the population in Basrah (Hagopian et al, 2010).

In Ninawa province, Al-Hashimi & Wang (2013) found that cancer IRR (for all types except leukemia) significantly decreased over the study period (1980-2010). These results stand in contradiction to the findings of the studies from Basrah governorate or from Fallujah. The discrepancy may be explained by the fact that Ninawa province, in Northern Iraq, has a different population, environment, economy, and history of conflict than Basrah governorate in Southern Iraq, or Fallujah. Unlike Basrah, Ninawa province was not directly impacted by armed conflict during the first Gulf War, although heavy fighting occurred in the capital Mosul during the US 2003 invasion, and Ninawa has been a continued focus of US military offensives against the Islamic State (Fathi, Matti et al. 2013). Al-Hashimi & Wang (2013) do not offer any hypothesis in their study as to why cancer incidence has decreased in the province during the study period. Possible factors that may affect the observable cancer incidence in Ninawa province include changes in demographics of the population due to migration or immigration (Thibos 2014), changes in life-expectancy due to the conflict (Rawaf, Hassounah et al. 2014), or decreased detection and registration capabilities due to conflict (Rawaf, Hassounah et al. 2014).

5.1.5 Cancer case counts

Case counts are an inappropriate method for investigating the impact of an environmental toxicant on population over time, because they do not account for changes in population size (e.g. population growth). As population grows, the number of cancer

cases diagnosed annually is expected to increase as well.

5.1.6 Cancer and uranium exposure case-control studies

Some of same potential methodological biases present in the birth defect and uranium exposure case-control studies are present in the cancer case-control studies. Three of the cancer case-control studies reported that their samples were recoded to ensure blinding, but one study did not (Al-Jobori et al, 2013). None of the four cancer case-control studies controlled for age or tobacco use in their analysis, though one study controlled for occupational exposure to uranium or ionizing radiation (occupational exposure was an exclusion criteria of the studies recruitment strategy for participants) (Al-Hamzawi et al, 2014).

Another problematic element unique to the cancer-case control studies is the possibility that the site of cancer (e.g. kidney cancer) or cancer treatment drugs could interrupt kidney function and lead to elevated levels of uranium in tissue samples *post facto*, even when environmental exposure to uranium is the same between cases and controls. The average daily intake of uranium is estimated to be 3.5 micrograms from food and water, and most of the absorbed uranium is filtered through the kidney and excreted in urine within 24 hours (Bleise, Danesi et al. 2003). Renal dysfunction and nephrotoxicity is a well-known adverse effect of many commonly used cancer treatment drugs (Kintzel 2001). No studies have been conducted on whether cancer treatment-induced nephrotoxicity is associated with elevated concentrations of heavy metals (or uranium) in

the blood or tissues, but the mechanism is plausible. None of the included studies reported whether cancerous tissues were collected before or during treatment.

5.1.7 Mixed outcome case-control studies

The definition of cases (exposed) and controls (unexposed) in the studies by Al-Hamadany et al (2012) was highly problematic and invalidates their study results.

5.1.8 BCL-2 expression and intensity

There are no published studies, to our knowledge, that discuss the mechanism by which uranium could alter BCL-2 expression, and the authors of the included study examining BCL-2 expression provide no hypothesis or explanation. However, it is known that BCL-2 expression varies with cancer stage, and the study acknowledges that low levels of health awareness in Iraq could lead Iraqi women to seek treatment at only an advanced cancer stage (Mohammad, 2016). Cancer stage was not a criteria for recruitment of either cases or controls. Additionally, the authors report that differences in tissue processing time, tissue quality, and timing for embedding tissues in paraffin between cases and controls may have impacted outcome measurements, but data is not available for those variables (Mohammad, 2016).

5.1.9 Immune system function

The study by Abdul-Wahid (2009) two important limitations that could potentially introduce bias into study results. First, the study's methodology requires manual counting of leukocyte concentrations by a lab technician, and the study did not report that samples

were recoded to ensure blinding. Second, the study did not account for important confounders known to be associated with white blood cell concentrations including sex, tobacco use, history of cancer or cardiovascular disease, or obesity (Kannel, Anderson et al. 1992, Dixon and O'Brien 2006).

Likewise, the case-control study of bullet wounds from Ramadi did not control for any confounders that could affect variables related to immune system function. Secondary infections related to bullet wounds, including gangrene (Peltola, Ahlqvist et al. 1986), could dramatically alter the parameters measured, and were not accounted for in the study.

Mryoush & Salim (2015) used a robust method for measuring uranium exposure among participants, but did not conduct an isotopic analysis to determine if the source of uranium was artificial or natural. The authors reported that the use of phosphate fertilizers, or proximity to fertilizer production facilities, could lead to higher concentrations or uranium in soil samples in the study area. The study did not account for other confounders that could affect Mitotic Index measurements among participants, including age, health status, and tobacco use (Yadav and Thakur 2000).

5.2 Added value of this systematic review

There exists a large volume of secondary literature (reviews, editorials, commentaries, or expert narratives) on the health impacts of depleted uranium in Iraq. Case-in-point, our SR search strategy captured nearly twice as many reviews as primary studies on the topic. During the full text screening phase of this SR, we found that 55 publications met our first three inclusion criteria (i.e. (a) reported or measured weaponized uranium in Iraq, (b) reported or assessed patient-important health outcomes (c) among the

Iraqi population). However, those publications did not contain or report primary research **(Appendix VI).**

Until now, the mantra in the literature has been that not enough studies have been conducted to assess whether depleted uranium has impacted public health in Iraq (Al-Hadithi 2012, Besic, Muhovic et al. 2018). For example, Al-Hadithi et al (2012) concluded that a lack of data prohibited their ability to draw conclusions about whether exposure to "DU or other teratogenic agents" has led to a higher rate of birth defects in Iraq. Notably, Al-Hadithi et al (2012) only reviewed a fraction of the relevant studies published in 2012 or earlier that were identified by this SR. In a meta-analysis of depleted uranium in the Middle East, Besic et al (2018) sought to correlate their findings with adverse public health outcomes in the region, using methods similar to those used in their previous study on the Balkan region (Besic et al, 2017). Their Middle East review captured only one study of an Iraqi population (Al-Dujaily et al, 2008). That study, incidentally, was also captured by this SR, but was excluded during the full text screening phase, because it did not measure association between uranium exposure and health impacts. Rather, it compared the expression of the HER-2/neu proto-oncogene between Iraqi breast cancer patients with malignant and benign tumors (Al-Dujaily et al, 2008). Like other reviews before it, Besic et al (2018) made the case that the "very low number" of human observational studies that they found made it impossible to evaluate the public health impacts of depleted uranium in Iraq or the region.

The findings from this SR allow us to make a new argument: the body of evidence does not lack studies, it lacks *high quality* studies. Our list of included studies for such a narrow topic is unexpectedly large, and the findings are relatively cohesive. Even so, no

conclusions about associations can be drawn. The high risk of bias prevalent across studies leads us to question their internal validity.

When we embarked on this systematic review, we expected to capture few studies meeting our inclusion criteria. We were prepared to announce a rallying cry over publication bias, or rather, publication repression. Afterall, there was ample evidence suggesting that politicization of DU science was interfering with research and publication (Lang 2001, Edwards 2004, Al-Fahaad 2012, Webster 2013).

What we found instead was a plethora of studies - the products of the tenacity of Iraqi scientists and their international counterparts. The systematic review methodology is that it "leaves no stone unturned", and we were able to assemble, in a single collection, more human observational studies investigating associations between exposure to weaponized uranium and health outcomes in Iraq than any publication had before. Three contact experts were contacted and asked to review our list of included studies – none of whom were aware of additional relevant studies. This point speaks to the sensitivity of the systematic review method.

But we also see in our findings the insufferable consequences of war and sanctions, not only on the health and well-being of Iraqi citizens, but in Iraqi medical research and health sciences, reflected in the high risk of bias across our included studies.

The humanitarian impacts of US military response to the Iraqi invasion of Kuwait in 1990, the near-total destruction of Iraqi civil infrastructure, coupled with the most austere sanctions in history, are well-rehearsed in the literature (Gordon 2010). The sanctions against Iraq, applied at a unipolar moment in global governance, effectively enforced famine on the Iraqi population and crippled the country's ability to rebuild public

infrastructure, leading to widespread malnutrition, maternal folate deficiency, high rates of infant mortality, and ecological devastation (Gordon 2010, Jones 2014).

What is less known is that the sanctions, specifically resolution 661, not only restricted the flow of physical goods and financial resources into and out of Iraq, but effectively acted as an intellectual embargo, devastating Iraq's medical research capacities (Richards and Wall 2000, Dewachi 2017). The UN sanctions imposed in 1990 were modified after the 2003 US invasion of Iraq, and then lifted in 2010. Even though the investigation of health impacts of DU has been a priority for Iraqi scientists since the early 90's, we found that the majority of our included studies (77%) were published in 2010 or later, after the sanctions had been lifted.

Under the sanctions, Iraqi medical institutions lost access to textbooks, peer-reviewed journals, and equipment (Richards and Wall 2000). The importation of medicine was allowed, but nearly everything else needed to surveil health in the population or train new medical researchers was blocked (Gordon 2010). All of our included studies which used specialized equipment (such as ICP-MS, or CR-39 fission track detectors) to measure uranium concentrations in human biological samples were published in 2011 or later. Additionally, the sanctions placed restrictions on the ability of Iraqi scientists to publish their research in international journals, and colleagues from institutions in the US and Europe were prohibited from traveling to Iraq to collaborate on research or offer trainings (Richards and Wall 2000). Only seven included studies in this systematic review were conducted by Iraqi researchers and published prior to 2010, all of which were published in Iraqi university journals.

Under these circumstances, the quality of Iraqi research could not but decline. Often seen as soft or nonviolent tools of global governance, economic sanctions and blockades debilitate health systems (even when exceptions are provided medicine), imposing a kind of invisible violence on effected populations; as our results suggest for the case of Iraq, sanctions hinder the ability of a nation to recover from and respond to the toxic remnants of war. This raises important concerns over contemporary sanctions and blockades applied against Iran, Yemen, Gaza, Syria, and elsewhere.

5.3 Strengths of this systematic review

The SR methodology (in general) has many strengths in and of itself, the SR conducted for this thesis (specifically) had many strengths. In conducting this SR, we comprehensively searched grey literature sources in addition to academic databases, a step that not all SRs practice, and we did not limit studies by language of publication, which proved to be particularly relevant for this topic, as many included studies were published only in Arabic (not English). In developing a highly sensitive search strategy, we were able to capture far more relevant studies than were captured in initial simple searches. Finally, our SR is able to provide a model for future SRs on associations between weaponized uranium exposure (or other environmental exposures) and adverse health outcomes among other war-impacted populations.

5.4 Limitations of this systematic review

As the demand for and the production rate of SRs has increased, the need for engaging stakeholders in the SR process has emerged (Haddaway, Kohl et al. 2017). This is particularly true in the realms of environmental management and public health, where the aim of SRs is ultimately to recommend or identify interventions or best practices. Like content experts, stakeholders can broaden the sensitive of a search strategy (by helping to identify more relevant literature), provide input into the appropriateness of interventions or recommendations, and broaden the impact and audience of an SRs results (Haddaway, Kohl et al. 2017). A limitation of this SR is that we did not adopt a framework or method for engaging stakeholders, such as concerned citizens or residents of DU impacted areas of Iraq. The main reason that stakeholders were not engaged as part of this thesis research was time constraints. As an academic research project, conducted under the auspices of the American University of Beirut, engaging stakeholders would include a lengthy ethics review process with the Institutional Review Board at AUB. Secondly, given the diverse breadth of knowledge on our SR team (including an Iraqi doctor and scholar, Omar Dewachi), the high sensitivity of our search strategy, and efforts at seeking input from content experts, we felt reasonably confident that no relevant studies were missed. To address this limitation, as a next step following the completion of this SR, we will seek to disseminate our findings to stakeholders.

5.5 Implications for future research

The sparsity of high quality human observational studies on the health impacts of DU among the Iraqi population prevents firm conclusions on strength and direction of associations from being drawn, but does not negate the possibility that DU weapons have

adversely affected public health in Iraq. We call on the international community to support Iraqi scientists, whose capabilities have been undermined by war, economic sanctions, and an intellectual embargo, as they advance research on this topic. Specifically, there is a need for primary human observational studies. Because of the low-incidence of many of the adverse effects that are plausibly induced by exposure to depleted uranium (including CBDs and leukemia), prospective cohort studies are not feasible. Case-control studies with rigorous methods of exposure measurement (e.g. biomarkers), adequate blinding of key personnel, and control for important confounders are needed. Such studies should not only report differences in means of uranium concentrations between samples from cases and controls, but calculate Odds-Ratios (ORs), in order to estimate effect size (e.g. strength of association).

Strength of association is only one of nine criteria for claiming that there is a causal relationship between an exposure (or intervention) and a public health outcome. The Bradford Hill Criteria, first published in 1965, remain the guiding principles for evaluating causality in public health today. The other eight principles are: consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. In order to establish consistency (reproducibility), associations between uranium exposure and adverse effect must be investigated among different populations or samples. Although the risk for methodological bias was found to be prevalent across our included studies, it is noteworthy to point out that the findings of association were highly consistent; 81% of our included studies (n=25) reported finding an association. One of the weaknesses of studies employing ecological study designs is that they do not meet the criteria of specificity. This is yet another reason why more high-quality observational studies are needed. Regarding

the principle of temporality, exposure must be shown to come before adverse effects. One of the strengths of ecological time trend studies is that their design allows them to test for temporality. Biological gradient (dose-response) is usually inferred from experimental studies, but can also be derived from observational studies if they assess strength of association (effect estimates) under varying exposure scenarios. Plausibility, as discussed in the Chapter II, is well established for this topic from in vivo and in vitro studies. The findings from our included human observational studies also show strong coherence (agreement with experimental studies). Regarding the principle of experimental evidence, such data cannot (and should not) be obtained, on ethical grounds. And finally, concerning analogy, there is a strong basis for assuming uranium is a causal factor in cancers and birth defects when compared to other heavy metals (including lead, mercury, and cadmium) for which the toxics effects are well known. Analogies can also be found among other populations exposed to chronic, low-dose radiation contamination, such as downwinder populations in the Southwestern United States, or populations affected by Chernobyl fallout in the Ukraine and Belarus.

This SR does not represent a systematic assessment of studies which measured uranium or radiologic contamination in Iraq without also assessing health outcomes. Although studies that estimated future health risks based on absorbed dose or effective dose calculated from environmental radioactivity measurements in Iraq (as opposed to reporting current health outcomes among participants or target populations) did not meet our inclusion criteria, they still offer insight into possible health hazards faced by the Iraqi population. Further, no systematic reviews or meta-analyses on evidence of uranium toxicity from animal studies, or on DU-exposed populations outside of Iraq (such as the

Balkans), have been conducted. Huge bodies of primary studies exist for these topics, but they have yet to be systematically synthesized and critically appraised. Given the diverse streams of evidence that can inform whether (and to what extent) weaponized uranium in a cause of cancer and disease in Iraq, more systematic reviews - the premier method for evidence synthesis - on the above mentioned topics should be conducted.

CHAPTER VI

RECOMMENDATIONS & CONCLUSION

"And it doesn't disappear the day the bombs disappear. It has to be dismantled, and in order to dismantle it you have to understand the dynamics of the ecology of war."

- Ghassan Abu-Sitta, MBchB, FRCS[2]

"Medicine must be political."

- Richard Horton[3]

6.1 Encourage more primary research

The results from this SR identified the need for more high quality human observational studies on the health impacts of weaponized uranium in Iraq (as outlined in Chapter V). How can such research be encouraged and supported? Two critical elements for encouraging health research by Iraqi scientists are: funding and research capacity (Rezaeian 2016). One venue for promoting health research and building research capacity in developing countries is the Special Programme in Research and Training in Tropical Diseases (TDR) within the WHO (WHO 2012). Operating in over 60 countries, including Iraq, the TDR is uniquely positioned to offer trainings and provide grants to Iraqi scientists to fill this research gap. Complementarily, an independent international research collaboration could play a major role in generating new research on this topic. *The Lancet*

[2] In interview with Andre Vltchek, published in *The Ecologist*, April, 2017: https://theecologist.org/2017/apr/28/ecology-war-imperial-power-permanent-conflict-and-disposable-humans
[3] Speaking at a conference for the Lancet Palestinian Health Alliance, held at the American University of Beirut in March, 2018

Palestinian Health Alliance (Watt, Giacaman et al. 2017) and *The Lancet – American University Beirut Commission on Syria* (Jabbour, Leaning et al. 2016) provide two guiding examples. The recent announcements that the US continues to use DU weapons in Iraq and Syria in 2017 (Oakford 2017) and the release of the Iraq War records in 2016 (Oakford 2016) should act as impetuses for creating and coordinating such a commission. Outside of Iraq (who' medical infrastructure is in a dismal state) medical centers where the Iraqi Ministry of Health issues referrals or subcontracts wards are strategic locations to promote and conduct primary research. Dewachi et al (2014) have described how protracted conflict in Iraq has driven citizens to travel abroad to seek medical care, a phenomenon which they coin "the therapeutic geography of war" (Dewachi, Skelton et al. 2014). The Iraqi Ministry of Health has a referral program to the American University of Beirut Hospital (AUBMC), and so AUB could be a decisive location to recruit study participants.

6.2 Update the ATSDR toxicity profile for uranium

The Agency for Toxic Substances and Disease Registry is the preeminent source for health practitioners in the US to seek relevant toxicological data. The toxicity profile for uranium (including depleted uranium) was written in 1999, and updated in 2013 (HHS 2013). While the profile is thorough (and was an essential source for obtaining information of the properties and biokinetics of uranium for this thesis), it has three weaknesses. First, ATSDR toxicity profiles are essentially expert narrative reviews; they do not review the literature systematically. This thesis has elaborated the argument on the strength (and necessity) of conducting systematic reviews in Evidence Based Medicine (Chapters II and

III), and has discussed the inherent limitations of narrative reviews. This deficiency may in part explain the second weakness that we have identified in the ATSDR's uranium profile: its failure to address the body of epidemiological studies on residents of warzones that have been exposed to depleted uranium. The ATSDR states that:

> *"No studies were found regarding the cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, metabolic, dermal, ocular, body weight, or other systemic effects in humans following chronic-duration inhalation exposure." (pg. 46)*

While it is true that no RCT's of chronic uranium exposure by inhalation exist (the highly unethical human experimental studies of uranium toxicity conducted in the 1940's all involved exposure via ingestion or injection) (Norton and Dellasanta 2016), this thesis has shown that there are ample human observational studies from the Balkans and Iraq, where residents of contaminated areas have been chronically exposed (primarily via inhalation) to uranium oxides (Al-Shammari 2016, Besic, Muhovic et al. 2017). Even if those studies employ imperfect methodologies, they deserve mention and review in the ATSDR profile, especially those that have been published in peer-reviewed journals.

The third, and perhaps most problematic, weakness with the ATSDR uranium profile is that it dismisses the radiologic and carcinogenic toxicity of the element. The ATSDR states:

> *"IARC [International Agency for Research on Cancer], the U.S. Department of Human and Health Services, and the NTP have not classified uranium as to its carcinogenicity." (pg. 360)*

It also repeatedly reiterates that uranium toxicity is not attributed to its radiologic properties:

> *"The health effects of natural and depleted uranium are due to chemical effects and not to radiation." (pg. 5)*
>
> *"The health effects associated with exposure to depleted uranium will be the same as natural uranium because the toxicity of natural uranium is primarily due to chemical toxicity to uranium rather than uranium radiotoxicity." (pg. 17)*
>
> *"Health effects associated with exposure to natural uranium appear to be solely chemical in nature and not radiological and the contribution of the radiation toxicity." (pg. 20)*
>
> *"The health effects associated with oral or dermal exposure to natural and depleted uranium appear to be primarily chemical in nature and not radiological, while those from inhalation exposure may also include a slight radiological component." (pg. 39)*

In fact, the International Agency for Research on Cancer (IARC) *has* classified internalized uranium as a Group 1 carcinogen (Armstrong, Brenner et al. 2012). IARC has five classifications for carcinogenic potential of evaluated substances, and Group 1 ("carcinogenic to humans") is reserved for substances with the highest tier of evidence. In 2012 (prior to the publication of the ATSDR's update of the uranium profile), IARC issued monograph 100D, which classified all internalized alpha-emitting isotopes (including natural and depleted uranium) as Group 1 carcinogens. By definition, the IARC's determination of the carcinogenicity of uranium is based on its radiologic (not chemical) properties – at odds with the ATSDR. Although the specific activity of depleted uranium is 40% lower than that of natural uranium (Bleise, Danesi et al. 2003), its radiological properties still pose health risks.

These misleading dismissals by the ATSDR (of uranium radiologic and carcinogenic properties) have the potential to negatively impact primary research, because funding agencies that refer to the ATSDR profile may deem studies investigating the radiologic toxicity of weaponized uranium to be irrelevant. Therefore, we believe that the ATSDR uranium profile is urgently due for an update.

6.3 Improve the healthcare system in Iraq

Thirty years of protracted war, foreign interventions, and twenty years of sanctions have debilitated Iraq - economically, politically, socially, environmentally, and medically (Webster 2016). Doctors and other health practitioners have been targeted by assassinations (Al-Kindi 2014), and many have fled the country leading to 'brain drain' (Dewachi, Skelton et al. 2014). These points are thoroughly rehearsed in the literature and have already been discussed at length in this thesis (Chapters II & V). If the use of weaponized uranium has led to adverse health outcomes in Iraq, and if the ultimate goal of establishing that causality is to generate recommendations for prevention and treatment, then redeveloping Iraq's healthcare system is imperative. Only with a robust healthcare system in place can early detection of cancers and birth defects take place, and treatments (such as drug therapy in the case of cancers, or surgical interventions in the case of infants born with CBDs) be implemented, thereby reducing the burden of disease on the Iraq population. Improved detection, surveillance, and registration of adverse health outcomes believed to be linked to uranium exposure could also help to identify potential 'hotspots', or areas that should be assessed for uranium contamination and targeted for clean-up

operations or other preventative measures. As an extension of the healthcare system, in the social-ecological model of health and well-being, the education system in Iraq also must be reconfigured to tailor to the needs of disabled students (including children born with CBDs), as has been argued by UK pediatrician Dr. Allison Alborz (Alborz 2013).

Providing precise recommendations for redeveloping the Iraqi healthcare system is beyond the scope of this thesis. However, it is pertinent to comment on the fact that the healthcare system (in any country) is part of a wider ecology, and improving the provision of health services cannot be achieved without examining to root causes of the systems' failures or 'de-development' (in Iraq particularly). Iraq's healthcare system, and the health of the population, cannot be mended without addressing the extremely high militarization in the country and the region, which is embedded within a global geo-political-economic context. The Arab world has the highest rate of weapons import per person of any region in the world (four times the global average), and the lowest ratio of healthcare to military spending of any region (El-Zein, Jabbour et al. 2014, El-Zein, DeJong et al. 2016). In fact, it is the only region where military expenditures exceed healthcare expenditures, as a fraction of GDP (El-Zein, Jabbour et al. 2014). But militarization in Iraq cannot be viewed in isolation. To put it diplomatically, militarization in Iraq and the Arab world:

> *"is a part of, and partly constrained by, a broader geopolitical and economic world order characterised by power asymmetry [and] (...) western countries sometimes play in perpetuating commercial, economic, and political practices that run counter to human development needs in the region."* (El-Zein, Jabbour et al. 2014)

6.4 Prevention through decontamination

Under the pretext of the precautionary principle, uranium exposure should be limited through the clean-up of contaminated sites (McDonald, Kleffner et al. 2008). Three methods exist for the removal of uranium from environmental media: active remediation, passive bioremediation, and natural attenuation. Active remediation involves the physical removal and isolation/storage of contaminated debris. It can include the act of relocating military scrap metal (e.g. tanks) to designated storage or burial sites, applying a 'suck, muck, and truck' method for contaminated surface soil, or employing the 'pump and treat' technique for ground water (Burroughs 2000). Passive bioremediation uses microbiota (bacteria and fungi) to decompose uranium compounds in soil or water, while natural attenuation uses chemical methods to adsorb uranium compounds to mineral compounds. In also includes phytoremediation, which has been identified as one of the most promising techniques for radiological rehabilitation of soil (Dubchak and Bondar 2019). The goal of both passive bioremediation and natural attenuation is primarily to convert soluble uranium compounds into stable insoluable forms, thereby reducing their environmental mobility, bioavailability, and toxicity – processes which do not involve the physical removal of uranium from environmental media (Selvakumar, Ramadoss et al. 2018). However, with plants possessing rhizofiltration capabilities, phytoextraction can be used to remove uranium compounds from soil and groundwater. Via this process, uranium compounds become concentrated in the above ground biomass, which can then be removed and disposed (Dubchak and Bondar 2019).

In Iraq, active remediation has taken place at DU impacted sites, primarily at tank battle sites, or along highways littered with vehicles destroyed by DU munitions

(Zwijnenburg 2013). However, these clean-up effort (most of which occurred between 2003-2005 under the Coalition Provisional Authority) has not been transparent or well-documented. It is unlikely that the clean-up, without guidance or leadership from international organizations like the IAEA, conformed to international standards for handling low-level radioactive waste (Zwijnenburg, Weir et al. 2014). Furthermore, without a complete list of sites targeted by DU munitions, or a comprehensive national survey of DU contamination, it is doubtful that active remediation has taken place at every 'hotspot' or DU-impacted site in the country (Zwijnenburg, Weir et al. 2014).

At any rate, active remediation may be an insufficient remediation technique in the Iraqi context. First, because disposal sites are themselves toxic hazards that have become sources for unregulated scrap-metal recycling (UNEP 2003, Zwijnenburg, Weir et al. 2014). Second, because by the time that scrap metal is removed, environmental media (air, water, and soil), have already been contaminated with uranium compounds. More than 80% of DU munitions fired from aircraft become embedded (meters deep) into soil, sand, and are not easily identified and removed (Handley-Sidhu, Keith-Roach et al. 2010). Overtime, they slowly corrode, releasing uranyl ions and other corrosion products into the soil and watershed. Of those that hit their target, 30-70% of their volume ignites and instantly oxidizes, creating uranium oxide aerosols which are dispersed in the air, and eventually deposited on soil surfaces (Handley-Sidhu, Keith-Roach et al. 2010). Given this information, and that UNEP detected depleted uranium in drinking waters sources in Southern Iraq (Åkerblom 2008), the use of bioremediation, including phytoremediation and natural attenuation should be explored.

6.5 International moratorium on the use of uranium in conventional weapons

Also under the domain of the precautionary principle, in the absence of high quality human observation studies (as identified by this thesis), a ban on the use of uranium in conventional weapons and munitions ought to be enacted (McDonald, Kleffner et al. 2008). Precedence for this type of ban has been set by the Ottawa Treaty (The Convention on the Prohibition of the Use, Stockpiling, Production and Transfer of Anti-Personnel Mines and on their Destruction), which came into effect in March 1999, and the Convention on Cluster Munitions, which came into effect in August 2010 (Wexler 2003). The 'deployment of shame' in transnational politics, and the coordination of international networks of NGOs (such as the International Campaign to Ban Landmines), played critical roles in the creation and ratification of those treaties (Wexler 2003). A similar strategy and international network for the ban of DU weapons already exists (the International Campaign to Ban Uranium Weapons, ICBUW) (Khamis, Ashraf et al. 2016), as well as political will at the level of the United Nations – six resolutions were passed at the UN General Assembly between 2007-2015, reaffirming concern over the health impacts of DU weapons (Faa, Gerosa et al. 2018).

So, why hasn't ban been set in place yet? Dr. Charli Carpenter (University of Massachusetts at Amherst) has argued that the lack of scrutiny applied to uranium weapons, relative to other banned weapons, is not due to priorities set by nation states, but rather due to decisions made by 'well connected international networks' which bear the greatest influence in creating weapons and arms-control agendas (Carpenter 2011).

It must be recognized that an international ban on uranium weapons does not guarantee a prevention of their use. The United States is not party to either the landmine or

cluster bomb treaty, and given its current continued use of DU weapons in Iraq and Syria, it is unlikely to sign on to a DU weapons ban. Nevertheless, public health professionals and practitioners have an obligation to support such a ban, in an effort to shape global political norms. The Union for Concerned Scientists and Physicians for Peace are two organizations that have taken official stances on nuclear (nonconventional) weapons, but have yet to do so on conventional uranium weapons. It is time for the global health community to do more to advocate for peace (McCoy 2016). They must join the call for a moratorium on uranium weapons.

In conclusion, this SR has constructed a narrative on the health impacts of depleted uranium, thoroughly searched and scrutinized the literature on human observational studies in Iraq, and found that despite interest on the part of Iraqi scientists, and a prolific number studies, the body of evidence lacks high quality studies. Therefore, this thesis has made recommendations for more primary research and suggested means by which that research could be encouraged or supported. It has also called for an update of the ATSDR toxicological profile for uranium, to reflect the current state of knowledge. Regarding prevention and treatment of adverse health outcomes, we have acknowledge the need to re-develop the Iraqi healthcare system (which cannot be done under the current state of militarization in the country and region), and implement thorough, transparent decontamination and remediation efforts at uranium impacted sites in the country. Finally, under the precautionary principle, we argue that the global health community has a responsibility to support a global ban on DU weapons.

APPENDIX I

SEARCH FUNCTIONS OF GREY LITERATURE DATABASES

1) WHO Digital Library (http://apps.who.int/iris/):

Notes on searching the database:

- Has advanced search features
- Takes Boolean operators (Note: without operators, the search automatically assumes "AND" between search terms. Meaning, "Iraq Uranium" yields the same results as "Iraq AND Uranium")
- Takes truncation, and use of parentheses
- Cannot restrict searches to titles and abstracts only
- To restrict results by date, must search each publication year separately

Notes on managing references:

- There is no way to download the results directly into a reference manager. They must be entered into EndNote manually.
- Only entered results that were published in 1990 or later were entered into EndNote.
- In cases where language duplicates exist (identical document number), only the English language document was entered into EndNote.

2) IAEA Scientific and Technical Publications (https://www-pub.iaea.org/books/)

Notes on searching the database:

- Has an Advanced Search option, but within the advanced search it accepts exact phrase only
- Does not take Boolean operators
- Does not take truncation
- To restrict results by date, must search each publication year separately

Notes on managing references:

- Results can be downloaded into a reference manager individually

- There is no way to bulk download results for import into EndNote, but they do not need to be entered manually

3) UNEP Knowledge Repository (http://web.unep.org/publications/):

Notes on searching the database:

- No Advanced Search options, but results can be filtered by year of publication, language, and document type
- Does not take Boolean operators
- Does not take truncation

Notes on managing references:

- There is no way to download the results directly into a reference manager. They must be entered into EndNote manually
- Note: not all results could be downloaded. In some cases, only title, publisher, abstract, and year of publication were visible

4) ProQuest Dissertation and Theses Global (Access through AUB Libraries):

Notes on searching the database:

- Advanced Search options
- Takes Boolean operators
- Can search Title, Abstract, and Keywords simultaneously, and am able to limit search results by year of publication

Notes on managing references:

- All results can be downloaded at once in RIS format

5) Google Scholar

Notes on searching the database:

- Has an Advanced Search option (limited)

Notes on managing references:

- An EndNote extension was used to export GoogleScholar results directly into EndNote

APPENDIX II

TITLE AND ABSTRACT SCREENING FORM

Does the publication report or measure uranium, its corrosion products, or ioni zing radiation in or surrounding areas?

(Uranium corrosion products may include uranium oxides and uranyl ions, while exposure to ionizing radiation may include alpha, beta, or gamma rays. Studies that only measure or report exposure to UV radiation (i.e. solar radiation) are excluded. Levels or concentrations of ionizaing radiation or uranium should be measured/reported in Iraq or surrounding areas such as Kuwait.)

☐ NO → Exclude
☐ Yes or uncertain → Go to the next question

Does the publication report or measure health outcomes or disease states in humans?

(Do not restrict to only birth outcomes at this stage.)

☐ NO → Exclude
☐ Yes or uncertain → Go to the next question

Is the study population Iraqi?

(Does the human population for which health outcomes are reported include or consist entirely of Iraqi nationals? Exclude studies that only report health outcomes in populations of military veterans (of the US or other nationalities) who fought during the 1990 or 2003 Iraq Wars.)

☐ NO → Exclude
☐ Yes or uncertain → Go to the next question

Does the publication include or report primary research?

(Exclude review articles, including systematic reviews, which do not contain or report primary research.)

☐ NO → Exclude
☐ Yes or uncertain → Get full text

APPENDIX III

FULL TEXT SCREENING FORM

Does the publication report or measure uranium, its corrosion products, or ionizing radiation in Iraq or surrounding areas?
Uranium corrosion products may include uranium oxides and uranyl ions, while exposure to ionizing radiation may include alpha, beta, or gamma rays. Studies that only measure or report exposure to UV radiation (i.e. solar radiation) are excluded. Levels or concentrations of ionizaing radiation or uranium should be measured/reported in Iraq or surrounding areas such as Kuwait.

☐ NO → Exclude, and note reason in Excel
☐ Yes → Go to the next question

Does the publication report or measure health outcomes or disease states in humans?
Do not restrict to only birth outcomes at this stage. Outcomes ought to be clinical or "patient important", i.e. exclude if they only measure uranium concentrations in human tissues.

☐ NO → Exclude, and note reason in Excel
☐ Yes → Go to the next question

Is the study population Iraqi?
Does the human population for which health outcomes are reported include or consist entirely of Iraqi nationals? Exclude studies that only report health outcomes in populations of military veterans (of the US or other nationalities) who fought during the 1990 or 2003 Iraq Wars.

☐ NO → Exclude, and note reason in Excel
☐ Yes → Go to the next question

Does the publication include or report primary research?
Exclude review articles, including systematic reviews, which do not contain or report primary research.

☐ NO → Exclude, and note reason in Excel
☐ Yes → Go to the next question

Does the study include a nonexposed (or lesser exposed) comparator or control group?
Exclude single-arm, non-comparator studies.

☐ NO → Exclude, and note reason in Excel
☐ Yes → INCLUDE

APPENDIX IV

THE NAVIGATION GUIDE INSTRUCTIONS FOR MAKING RISK OF BIAS DETERMINATIONS

1. Was the strategy for recruiting participants consistent across study groups?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

Protocols for recruitment and inclusion/exclusion criteria were applied similarly across study groups, and any one of the following:

- Study participants were recruited from the same population at the same time frame; or
- Study participants were not all recruited from the same population, but proportions of participants from each population in each study group are uniform

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about participant selection to permit a judgment of 'YES', but there is indirect evidence that suggests that participant recruitment and inclusion/exclusion criteria was consistent, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias)

Any one of the following:

- Protocols for recruitment or inclusion/exclusion criteria were applied differently across study groups; or
- Study participants were recruited at different time frames; or
- Study participants were recruited from different populations and proportions of participants from each population in each study group are not uniform

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about participant selection to permit a judgment of 'NO', but there is indirect evidence that suggests that participant recruitment or inclusion/exclusion criteria was inconsistent, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that participant selection is not an element of study design capable of introducing risk of bias in the study.

2. Was knowledge of the exposure groups adequately prevented during the study?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; or
- Blinding of key study personnel ensured, and unlikely that the blinding could have been broken; or
- Some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about blinding to permit a judgment of 'YES', but there is indirect evidence that suggests the study was adequately blinded, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

Any one of the following:

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; or
- Blinding of key study personnel attempted, but likely that the blinding could have been broken; or
- Some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about blinding to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not adequately blinded, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that blinding is not an element of study design capable of introducing risk of bias in the study.

3. Were exposure assessment methods robust?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

The reviewers judge that there is low risk of exposure misclassification and any one of the following:

- There is high confidence in the accuracy of the exposure assessment methods; or
- Less-established or less direct exposure measurements are validated against well-established or direct methods AND if applicable, appropriate QA/QC for methods are described and are satisfactory, with at least three of the following items reported, or at least two of the following items reported plus evidence of satisfactory performance in a high quality inter-laboratory comparison: Limit of detection or quantification; standards recovery; measure of repeatability; investigation and prevention of blanks contamination.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about the exposure assessment methods to permit a judgment of 'YES', but there is indirect evidence that suggests that methods were robust, as described by the criteria for a judgment of 'YES'. Studies only reporting that the QA/QC items above were satisfactory but not reporting all of the actual numbers may receive a judgment of "probably yes."

Criteria for the judgment of 'NO' (i.e. high risk of bias):

The reviewers judge that there is high risk of exposure misclassification and any one of the following:

- There is low confidence in the accuracy of the exposure assessment methods; or
- Less-established or less direct exposure measurements are not validated and are suspected to introduce bias that impacts the outcome assessment (example: participants are asked to report exposure status retrospectively, subject to recall bias)
- Uncertain how exposure information was obtained

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about the exposure assessment methods to permit a judgment of 'NO', but there is indirect evidence that suggests that methods were not robust, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that exposure assessment is not an element of study design capable of introducing risk of bias in the study.

4. Was confounding adequately addressed?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

The study accounted for (i.e., matched, stratified, multivariate analysis or otherwise statistically controlled for) important potential confounders, or reported that potential confounders were evaluated and omitted because inclusion did not substantially affect the results. The determination of specific confounders may be informed by the data, including the studies included in the review.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

The study accounted for most but not all of the important potential confounders AND this lack of accounting is not expected to introduce substantial bias.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

The study did not account for or evaluate important potential confounders.

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

The study accounted for some but not all of the important potential confounders AND this lack of accounting may have introduced substantial bias.

5. Were incomplete outcome data adequately addressed?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

Participants were followed long enough to obtain outcome measurements and any one of the following:

- No missing outcome data; or
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); or
- Missing outcome data balanced in numbers across exposure groups, with similar reasons for missing data across groups; or

- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a biologically relevant impact on the intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a biologically relevant impact on observed effect size; or
- Missing data have been imputed using appropriate methods

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about incomplete outcome data to permit a judgment of 'YES', but there is indirect evidence that suggests incomplete outcome data was adequately addressed, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

Participants were not followed long enough to obtain outcome measurements OR any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across exposure groups; or
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce biologically relevant bias in intervention effect estimate; or
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce biologically relevant bias in observed effect size; or
- Potentially inappropriate application of imputation.

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about incomplete outcome data to permit a judgment of 'NO', but there is indirect evidence that suggests incomplete outcome data was not adequately addressed, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that incomplete outcome data is not capable of introducing risk of bias in the study.

6. Are reports of the study free of suggestion of selective outcome reporting?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

All of the study's pre-specified (primary and secondary) outcomes outlined in the protocol, methods, abstract, and/or introduction that are of interest in the review have been reported in the pre-specified way.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information about selective outcome reporting to permit a judgment of 'YES', but there is indirect evidence that suggests the study was free of selective reporting, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

Any one of the following:

- Not all of the study's pre-specified primary outcomes (as outlined in the protocol, methods, abstract, and/or introduction) have been reported; or
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; or
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect); or
- One or more outcomes of interest are reported incompletely

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information about selective outcome reporting to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of selective reporting, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that selective outcome reporting is not capable of introducing risk of bias in the study.

7. Was the study apparently free of other problems that could put it at a risk of bias?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

The study appears to be free of other sources of bias.

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information to permit a judgment of 'YES', but there is indirect evidence that suggests the study was free of other threats to validity.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

There is at least one important risk of bias. For example, the study:

- Had a potential source of bias related to the specific study design used; or
- Stopped early due to some data-dependent process (including a formal-stopping rule); or
- Had extreme imbalance of characteristics among exposure groups; or
- Had differential surveillance for outcome between exposure groups or between exposed/unexposed groups
- The conduct of the study is affected by interim results (e.g. recruiting additional participants from a subgroup showing greater or lesser effect); or
- An insensitive instrument is used to measure outcomes (which can lead to under-estimation of both beneficial and harmful effects); or
- Selective reporting of subgroups; or • Has been claimed to have been fraudulent; or
- Had some other problem

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):
There is insufficient information to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of other threats to validity, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that other potential threats to validity are not capable of introducing
risk of bias in the study.

8. Was the study free of support from a company, study author, or other entity having a financial interest in any of the exposures studied?

Criteria for a judgment of 'YES' (i.e. low risk of bias):

The study did not receive support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples include the following:

- Funding source is limited to government, non-profit organizations, or academic grants funded by government, foundations and/or non-profit organizations;
- Chemicals or other treatment used in study were purchased from a supplier;
- Company affiliated staff are not mentioned in the acknowledgements section;
- Authors were not employees of a company with a financial interest in the outcome of the study;
- Company with a financial interest in the outcome of the study was not involved in the design, conduct, analysis, or reporting of the study and authors had complete access to the data;
- Study authors make a claim denying conflicts of interest;
- Study authors are unaffiliated with companies with financial interest, and there is no reason to believe a conflict of interest exists;
- All study authors are affiliated with a government agency (are prohibited from involvement in projects for which there is a conflict of interest or an appearance of conflict of interest).

Criteria for the judgment of 'PROBABLY YES' (i.e. probably low risk of bias):

There is insufficient information to permit a judgment of 'YES', but there is indirect evidence that suggests the study was free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of 'YES'.

Criteria for the judgment of 'NO' (i.e. high risk of bias):

The study received support from a company, study author, or other entity having a financial interest in the outcome of the study. Examples of support include:

- Research funds;
- Chemicals provided at no cost;
- Writing services;
- Author/staff from study was employee or otherwise affiliated with company with financial interest;
- Company limited author access to the data;
- Company was involved in the design, conduct, analysis, or reporting of the study;
- Study authors claim a conflict of interest

Criteria for the judgment of 'PROBABLY NO' (i.e. probably high risk of bias):

There is insufficient information to permit a judgment of 'NO', but there is indirect evidence that suggests the study was not free of support from a company, study author, or other entity having a financial interest in the outcome of the study, as described by the criteria for a judgment of 'NO'.

Criteria for the judgment of 'NOT APPLICABLE' (risk of bias domain is not applicable to study):

There is evidence that conflicts of interest are not capable of introducing risk of bias in the study.

APPENDIX V

PRISMA STATEMENT

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3, Panel
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2, 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4, Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2, 3, Appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, 5, Appendix
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any	5

		processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, Table 3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5, Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	No meta-analysis was conducted

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5, Appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No meta-analysis was conducted
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, Table 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, Figure 4a & 4b, Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No meta-analysis was conducted
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7, Figure 4a & 4b

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	No meta-analysis was conducted
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9, Panel
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2, 5

APPENDIX VI

FULL TEXT EXCLUSION JUSTIFICATIONS

Exclude – Exposure Study did not measure or report exposure to weaponized uranium in Iraq	[1-33]
Exclude – Outcome Study did not measure or report patient-important health outcomes	[34-76]
Exclude – Population Study population was not Iraqi	[77-102]
Exclude – Primary research Study did not contain original data or analysis	[103-157]
Exclude – Study Design Non-comparator study	[158-177]

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2. Gousheh, J.R., M., *[War injuries of the femoral nerve. Apropos of a series of 27 cases].* Annales de Chirurgie Plastique et Esthetique. **36**(6): p. 527-31.
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APPENDIX VI

RISK OF BIAS ASSESSMENTS FOR INCLUDED STUDIES

Table S1. Risk of bias assessment for Abdul-Wahid (2009)

Domain	Rating	Justification
Recruitment	Probably high risk	Study lacks complete description of recruitment criteria, but it is suggested that participants from the unexposed population were selected to be predisposed towards normal ("healthy") immune system function, while the same criteria was not applied to the selection of participants from the exposed population.
Blinding	High risk	Study does not report blinding of key personnel (e.g. personnel counting the number of labeled cells).
Exposure Assessment	High risk	The city of Baghdad does not represent an unexposed geographic location with certainty, as heavy fighting took place in the city during the 2003 invasion by US and coalition forces.
Confounding	Probably low risk	Control group subjects were age-matched, but it is unclear if sex was controlled for (control group was all males, but it is not explicitly stated that the exposed group was also all males).
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Low risk	The study is free of suggestion of selective outcome reporting. All of the study's specified outcomes were adequately reported.

Other Bias	High risk	The study reportedly performed t-test to measure association between cases and controls, but the p-values for the test were reported inaccurately.
Conflict of Interest	Low risk	The authors report no conflict of interest, and associated funds and persons appear to be from government and/or academia only.

Table S2. Risk of bias assessment for Alaani et al (2012)

Domain	Rating	Justification
Recruitment	High risk	Recruitment strategies for the control populations are not described.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Probably high risk	While Egypt (Giza) and Jordan represent unexposed populations, depleted uranium has previously been detected in Kuwait.
Confounding	High risk	No confounding variables were accounted for between study groups.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Low risk	The study is free of suggestion of selective outcome reporting. All of the study's specified outcomes were adequately reported.
Other Bias	Probably low risk	The method for assessing the incidence of congenital birth defects per 1000 live births in Fallujah was not precise (the denominator was estimated), but the explanation provided in the report suggests that the method was reasonably accurate.
Conflict of Interest	High risk	Authors report no conflict of interest, but funding for the study was partially provided by Swedish non-profit International Foundation for Research on Radiation Risk (IFRRR), which has a stated agenda of disputing the ICRP radiation risk model.

Table S3. Risk of bias assessment for Alaani et al (2011)a (Study 1)

Domain	Rating	Justification
Recruitment	High risk	Participants were recruited from different populations (Iraq and Israel). The description of the recruitment strategy for the Israeli population is not reported, nor is the recruitment criteria for Fallujah participants fully reported.
Blinding	Low risk	Hair samples for uranium concentration analysis were re-coded to ensure blinding of key personnel.
Exposure Assessment	Low risk	The method of uranium concentration measurement in hair samples (ICMPS) is robust.
Confounding	High risk	Study controlled for age but not sex in comparison between case and control group participants.
Incomplete Outcome Data	High risk	Birth outcomes were not reported for the control group (Israeli).
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	Low risk	The study appears to be free of other sources of bias.
Conflict of Interest	High risk	Authors report no conflict of interest, but funding for the study was partially provided by Swedish non-profit International Foundation for Research on Radiation Risk (IFRRR), which has a stated agenda of disputing the ICRP radiation risk model.

Table S4. Risk of bias assessment for Alaani et al (2011)b (Study 2)

Domain	Rating	Justification
Recruitment	High risk	Participants were recruited from different populations (Iraq and Sweden). The description of the recruitment strategy for the Swedish population is not reported, nor is the recruitment criteria for Fallujah participants fully reported.
Blinding	Low risk	Hair samples for uranium concentration analysis were re-coded to ensure blinding of key personnel.
Exposure Assessment	Low risk	The method of uranium concentration measurement in hair samples (ICMPS) is robust.
Confounding	High risk	Neither age nor sex were controlled for in comparison between case and control group participants.
Incomplete Outcome Data	High risk	Birth outcomes were not reported for the control group (Swedish).
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	Low risk	The study appears to be free of other sources of bias.
Conflict of Interest	High risk	Authors report no conflict of interest, but funding for the study was partially provided by Swedish non-profit International Foundation for Research on Radiation Risk (IFRRR), which has a stated agenda of disputing the ICRP radiation risk model.

Table S5. Risk of bias assessment for Alborz (2013)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	High risk	Self-reported exposure to war contamination is not a robust method of measuring uranium exposure.
Confounding	High risk	Study did not account for maternal age or consanguinity in analysis.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Low risk	Study appears free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S6. Risk of bias assessment for Al-Hamadany et al (2012)a (Study 1)

Domain	Rating	Justification
Recruitment	Probably low risk	Study lacks a complete description of recruitment methods.
Blinding	High risk	Blinding of key personnel for outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	Low risk	The method for uranium exposure measurement (CR-39 fission track detector) is robust.
Confounding	High risk	Study did not control for any confounders.
Incomplete Outcome Data	Low risk	Study appears to be free of missing outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	High risk	The study did not report uranium concentrations for all six study groups. The decision to lump occupationally exposed individuals, and healthy individuals living in neighborhoods suspected to be contaminated with depleted uranium, into the same group as cancer patients and mothers who gave birth to children with CBDs (cases) for comparison to the health, unexposed group, introduces a serious methodological flaw into the study.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S7. Risk of bias assessment for Al-Hamadany et al (2012)b (Study 2)

Domain	Rating	Justification
Recruitment	Probably low risk	Study lacks a complete description of recruitment methods.
Blinding	High risk	Blinding of key personnel for outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	High risk	The study defined uranium "exposed" cases as cancer patients, mothers of children with CBDs, employees of the Institute and Hospital of Radiotherapy and Nuclear Medicine, or individuals residing in areas of Baghdad identified by UNEP as contaminated. This is a highly problematic definition of "exposed".
Confounding	High risk	Study did not control for any confounders.
Incomplete Outcome Data	Low risk	Study appears to be free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes were reported.
Other Bias	Low risk	Study appears to be free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S8. Risk of bias assessment for Al-Hamzawi et al (2015)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Low risk	Tissue samples for uranium concentration analysis were re-coded to ensure blinding of key personnel.
Exposure Assessment	Low risk	The methods for uranium concentration measurement in blood samples (CR-39 fission track detector) are robust.
Confounding	High risk	Age and gender of subjects were reported, but not accounted for in statistical analysis.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	High risk	Neither the time frame during which tissue samples of cancer patients (cases) were collected by the histopathology clinic, nor the year that cancer was diagnosed for study subjects are reported. Cancerous tissue samples collected before 1991 or 2003, or collected from patients who were diagnosed before 1991 or 2003, cannot inform the question of whether uranium exposure (independent variable) is association with cancer (dependent variable). Samples from patients with inherited-type cancers also cannot inform the question of association. Some cancer treatment drugs can affect kidney function, which could hypothetically reduce the excretion rate of uranium, leading to higher concentrations of uranium in tissues among patients receiving treatment than in healthy volunteers, although the levels of environmental exposure may be the

		same. Likewise, cancer of the kidney can impair kidney function, leading to a reduction in the rate of uranium excretion and an accumulation of uranium in kidney tissues.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S9. Risk of bias assessment for Al-Hamzawi et al (2014)

Domain	Rating	Justification
Recruitment	Probably low risk	Study participants were not all recruited from the same population, but proportions of participants from each population in each study group are uniform. Study lacks a complete description of recruitment methods, but otherwise no reason to suspect there were substantial differences between comparison groups other than uranium exposure.
Blinding	Low risk	Blinding methods are not reported, but the authors of this SR judge that the neither the outcome and the outcome measurement, nor exposure and exposure measurement are likely to be influenced by lack of blinding.
Exposure Assessment	Low risk	The methods for uranium concentration measurement in blood samples (CR-39 fission track detector) are robust.
Confounding	Low risk	Age and sex were accounted for.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	High risk	Neither the year that blood samples of leukemia patients were collected by hospitals, nor the year that cancer was diagnosed for the leukemia patients are reported. Leukemia blood samples collected before 1991 or 2003, or collected from patients who were diagnosed before 1991 or 2003, cannot inform the question of whether uranium exposure (independent variable) is association with leukemia (dependent variable). Samples from patients with inherited-type leukemia also cannot inform the question of association. Some leukemia

		treatment drugs can affect kidney function, which could hypothetically reduce the excretion rate of uranium, leading to higher concentrations of uranium in blood among patients receiving treatment than in healthy volunteers, although the levels of environmental exposure may be the same.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S10. Risk of bias assessment for Al-Hashimi & Wang (2013)

Domain	Rating	Justification
Recruitment	Probably low risk	Data for this study was obtained from the Directorate of Health in Ninawa. The methods by which the Directorate collected the data between years was not reported, but there is no suggestion that methods of data collection differed between years.
Blinding	Not applicable	As a purely statistical analysis, blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Low risk	Given the study design (ecological: time trend), the method of exposure measurement in this study (year) is robust.
Confounding	Low risk	Age and sex were controlled for in the data analysis, as well as cancer type.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Low risk	The study is free of suggestion of selective outcome reporting. All of the study's specified outcomes were adequately reported.
Other Bias	Low risk	The study appears to be free of other sources of bias.
Conflict of Interest	Low risk	The authors report no conflict of interest, and associated funds and persons appear to be from government and/or academia only.

Table S11. Risk of bias assessment for Al-Jobori (2013)

Domain	Rating	Justification
Recruitment	High risk	Participants were not recruitments not recruited from the same population. The timeframe during which participants were recruited is not reported.
Blinding	High risk	Blinding of key personnel for outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	Probably high risk	While the method used for uranium concentration measurement in tissues samples (CR-39 fission track detector) is robust, the finding that control samples contained no detectable levels of uranium is highly questionable.
Confounding	High risk	Study did not account for any confounders.
Incomplete Outcome Data	Low risk	Study appears free from missing outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	High risk	The study did not clearly state whether the specimens were collected from affected organs. The sample size was small (controls, n=3).
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S12. Risk of bias assessment for Al-Rudainy et al (2011)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Probably high risk	The time frame for this study was 2004-2009, and thus no data for an unexposed population (prior to 1991 or 2003) was used in this study. The assumption that later year of diagnosis (more recent) equates with higher uranium exposure is questionable.
Confounding	Low risk	Study accounted for changes in population size in Basrah over the study period.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Low risk	Study appears free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S13. Risk of bias assessment for Al-Rudainy et al (2009)i

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Probably low risk	Given the study design (ecological: geographic comparison), the method of exposure measurement in this study (meta-synthesis of DU impacted sites) is robust.
Confounding	Probably low risk	Study did not account for any confounders in analysis, but there is no suggestion that confounders (such as age of population) differed between groups (districts) in the study area (Basrah Governorate).
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Low risk	Study appears free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S14. Risk of bias assessment for Al-Rudainy et al (2009)ii

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Probably high risk	The time frame for this study was 2007-2009, and thus no data for an unexposed population (prior to 1991 or 2003) was used in this study. The assumption that later year of diagnosis (more recent) equates with higher uranium exposure is questionable.
Confounding	Low risk	Study accounted for changes in population size in Basrah over the study period.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Low risk	Study appears free of other sources of bias.
Conflict of Interest	Low risk	Authors declared no conflict of interest. Associated funds and persons appear to be from academia only and free of financial interests in study results.

Table S15. Risk of bias assessment for Al-Sabbak et al (2012)a (Study 1)

Domain	Rating	Justification
Recruitment	Low risk	Recruitment criteria were consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	High risk	The control period (1994) does not represent an unexposed period, as depleted uranium weapons were used in Basra by US forces in 1991. The impact of economic sanctions in Iraq on health care infrastructure during that period (1994) may have impacted cancer surveillance and registration.
Confounding	High risk	No confounding variables in the study population were measured or accounted for.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Low risk	The study is free of suggestion of selective outcome reporting. All of the study's specified outcomes were adequately reported.
Other Bias	High risk	Only a fraction of the total births in Al-Basrah take place in a hospital setting, or at Al-Basra Maternity hospital specifically, which could introduce a form of selection bias into the study deign.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S16. Risk of bias assessment for Al-Sabbak et al (2012)b (Study 2)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	High risk	The study does not discuss blinding of key personnel (e.g. personnel conducting ICPMS analysis), and it is possible that lack of blinding could introduce bias.
Exposure Assessment	Probably low risk	The method of uranium concentration measurement in hair samples (ICMPS) is robust, as long as hair samples were collected from the scalp (not specified in study).
Confounding	High risk	Data on consanguinity was collected for study subjects, but maternal age was not.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Low risk	The study is free of suggestion of selective outcome reporting. All of the study's specified outcomes were adequately reported.
Other Bias	Low risk	The study appears to be free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S17. Risk of bias assessment for Al-Sadoon et al (1999)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Low risk	Given the study design (ecological: time trend), the method of exposure measurement in this study (year) is robust.
Confounding	High risk	Study did not account for maternal age or consanguinity.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Low risk	Study appears free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S18. Risk of bias assessment for Al-Sahlanee et al (2017)

Domain	Rating	Justification
Recruitment	Probably low risk	Study lacks a complete description of recruitment criteria. Namely, it does not specify if participants were recruited from a single hospital or multiple hospitals in Baghdad, or explicitly define the time period during which participants were recruited.
Blinding	High risk	The study does not discuss blinding of key personnel (e.g. personnel counting CR-39 fission detector tracks), and it is possible that lack of blinding could introduce bias.
Exposure Assessment	Low risk	The methods for measuring uranium concentration measurement in blood samples (CR-39 fission track detector) are robust.
Confounding	Probably low risk	Data on important confounders were collected, and it is suggested (but not explicitly stated) that they were controlled for in the adjusted regression analysis.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All of the pre-specified outcomes are reported.
Other Bias	Low risk	The study appears to be free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S19. Risk of bias assessment for Al-Sahlanee et al (2016)

Domain	Rating	Justification
Recruitment	High risk	Study lacks a complete description of recruitment criteria. Participants were recruited from different populations, and the number of participants from each population are not reported. The time period during which blood samples were collected from participants is not reported.
Blinding	High risk	Blinding of key personnel (e.g. personnel conducting track density counts) was not reported.
Exposure Assessment	Low risk	The method of uranium concentration measurement in maternal and umbilical cord blood samples (CR-39 fission track detector) is robust.
Confounding	High risk	Data on maternal age was collected, but not controlled for in analysis.
Incomplete Outcome Data	Low risk	The study did not have incomplete outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	Low risk	The study appears to be free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S20. Risk of bias assessment for Busby et al (2010)a (Study 1)

Domain	Rating	Justification
Recruitment	Probably low risk	Recruitment criteria was applied similarly across study groups. The response rate for the household survey was reportedly 70%, and the majority of the non-responses came from a single neighborhood where household residents were suspicious of the surveyors. The study authors provide a reasonable explanation that the non-responses were unlikely to be related to exposures or outcomes.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Low risk	Given the study design (cross-sectional), the method of exposure measurement in this study (year) is robust.
Confounding	High risk	The study does not account for maternal nutrition status as an important confounder.
Incomplete Outcome Data	Probably low risk	The study does not report any missing data (but they also do not report that all questionnaires were completed in full).
Selective Reporting	High risk	The study does not report the birth-sex ratio for age cohorts above 19 years. The next age cohort (20-24 years) has a birth-sex ratio even lower than the 0-4 years age cohort (776 compared to 860 males per 1000 females, respectively).
Other Bias	High risk	The study design was also potentially subject to recall bias or overreporting bias. Differential child mortality rates between sexes could also impact outcomes measured.
Conflict of Interest	Low risk	Authors declare no conflict of interest.

Table S21. Risk of bias assessment for Busby et al (2010)b (Study 2)

Domain	Rating	Justification
Recruitment	High risk	The recruitment strategies differed between exposed (Fallujah) and unexposed (Egypt) populations.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Low Risk	Egypt represents an unexposed population.
Confounding	High risk	Infant mortality rates have also been shown to be associated with a large number of social-ecological factors including environmental exposures, maternal malnutrition, poverty, and poorly functioning health care systems. These factors almost certainly differed between Fallujah and the control populations in Egypt, Jordan, and Kuwait, and were not accounted for in the study's analysis.
Incomplete Outcome Data	Probably low risk	The study does not report any missing data (but they do not report that all questionnaires were completed in full). The study suggests that parents may have underreported cases of birth defects, but the study accounted for that by collecting data on still births (with the reasonable assumption that families effected by stigma surrounding birth defects would report cases as still births or infant mortality).
Selective Reporting	Probably high risk	The questionnaire used in the study aimed to collected data on health status, birth history, and infant mortality among study participants for a ten year period, but only the most recent five year period was reported.
Other Bias	High risk	The method of data collection among the exposed population (Fallujah) was potentially subject to recall bias or overreporting bias.

Conflict of Interest	Low risk	Authors declare no conflict of interest.

Table S22. Risk of bias assessment for Busby et al (2010)c (Study 3)

Domain	Rating	Justification
Recruitment	High risk	The recruitment strategies differed between exposed (Fallujah) and unexposed (Egypt) populations.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Low Risk	Egypt represents an unexposed population.
Confounding	High risk	Age, but not sex, was controlled for in analysis of cancer rates.
Incomplete Outcome Data	Probably low risk	The study does not report any missing data (but they do not report that all questionnaires were completed in full).
Selective Reporting	Probably high risk	The questionnaire used in the study aimed to collected data on health status, birth history, and cancer history among study participants for a ten year period, but only the most recent five year period was reported.
Other Bias	High risk	The method of data collection among the exposed population (Fallujah) was potentially subject to recall bias or overreporting bias.
Conflict of Interest	Low risk	Authors declare no conflict of interest.

Table S23. Risk of bias assessment for Hagopian et al (2010)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Probably high risk	The time frame for this study was 1993-2007, and thus no data for an unexposed population (prior to 1991) was used in this study. The assumption that later year of diagnosis (more recent) equates with higher uranium exposure is questionable.
Confounding	Low risk	Study accounted for changes in population size in Basrah over the study period.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Probably high risk	The population of Basrah experience many other leukemogenic war-related exposures during the period 1993-2007, which may have also contributed to the observed increase in childhood leukemia.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S24. Risk of bias assessment for Hassan et al (2005)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	Probably high risk	The cancer registry from which data was obtained for this study was created in 1997, and thus no data for an unexposed population was used in this study. The assumption that later year of diagnosis (more recent) equates with higher uranium exposure is questionable.
Confounding	High risk	Study does not account for average age of population between years (increase in cancer rate is expected with an ageing population).
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Low risk	Study appears free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S25. Risk of bias assessment for Humaidi & Khalaf (2011)

Domain	Rating	Justification
Recruitment	Probably low risk	Study lacks a complete description of recruitment methods, but otherwise no reason to suspect there were substantial differences between comparison groups other than uranium exposure (as defined within the context of the study).
Blinding	High risk	Blinding of key personnel for outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	High risk	Not all bullets used by US or coalition forces contain weaponized uranium.
Confounding	High risk	Study does not account for age, severity of bullet injury, or location of injury.
Incomplete Outcome Data	Low risk	Study has no suggestion of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes were reported.
Other Bias	Low risk	Study appears to be free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S26. Risk of bias assessment for Mohammad (2016)

Domain	Rating	Justification
Recruitment	Probably low risk	Study lacks complete description of recruitment criteria for each population, but it is reported that samples were collected from patients in both populations during the same time frame.
Blinding	High risk	Blinding of key personnel for outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	Low risk	The Italian control population represents an appropriate (unexposed) control.
Confounding	High risk	Bcl-2 expression varies with cancer stage, and the study did not account for stage of breast cancer in analysis. Study suggests that this can be an important confounding variable, particularly because low levels of health education in Iraq could lead women to seek medical attention only at an advanced stage of cancer.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	Probably high risk	The study reports that the difference in tissue processing time, the difference in tissue quality, and the timing for embedding tissues in paraffin may have impacted outcome measurements, but data is not available for those variables.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S27. Risk of bias assessment for Mryoush & Salim (2015)

Domain	Rating	Justification
Recruitment	Probably low risk	Study lacks a complete description of recruitment criteria, but otherwise no reason to suspect there were substantial differences between comparison groups other than uranium exposure.
Blinding	High risk	Blinding of key personnel for either exposure or outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	Low risk	The method of measuring uranium concentration in soil samples (CR-39 fission track detector) is robust.
Confounding	Probably low risk	Age was controlled for and sex was not controlled for, but participants appeared to evenly distributed with regard to sex.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All of the pre-specified outcomes are reported.
Other Bias	High risk	The authors of the study reported that the use of phosphate fertilizers, or proximity to fertilizer production facilities, could lead to higher concentrations or uranium in soil samples in the study area.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from government and/or academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S28. Risk of bias assessment for Neamah & Tawfiq (2015)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	High risk	The city of Baghdad does not represent an unexposed geographic location with certainty, as heavy fighting took place in the city during the 2003 invasion by US and coalition forces.
Confounding	High risk	The study does not report or account for maternal age or consanguinity.
Incomplete Outcome Data	Probably low risk	The data in this study is presented in the form of matrices prepared for statistical analysis, from which missing outcome data cannot be interpreted. The authors do not report any missing outcome data in the narrative text.
Selective Reporting	High risk	The study does not report total number of births at each hospital.
Other Bias	Low risk	The study appears free of other sources of bias.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S29. Risk of bias assessment for Salman (2008)

Domain	Rating	Justification
Recruitment	Low risk	The strategy for recruiting participants was consistent across study groups.
Blinding	Not applicable	Blinding is not an element of study design capable of introducing risk of bias in the study.
Exposure Assessment	High risk	Study findings may reflect changes in cancer detection (diagnostic abilities), and not true change of cancer incidence in the population.
Confounding	High risk	Study does not account for average age of population between years (increase in cancer rate is expected with an ageing population).
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Low risk	All pre-specified outcomes are reported.
Other Bias	High risk	Study reports cases, not incidence of cancer.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S30. Risk of bias assessment for Savabieasfahani et al (2016)

Domain	Rating	Justification
Recruitment	High risk	Participants from the control group (children without CBDs) were selected from populations outside of Iraq.
Blinding	High risk	Blinding of key personnel for outcome measurement is not reported, and lack of blinding could introduce bias.
Exposure Assessment	Probably high risk	The method selected for exposure assessment (elemental bioimaging using LA-ICP-MS) may have a detection limit above the expected range of uranium concentration in human teeth.
Confounding	High risk	Age and sex were not accounted for.
Incomplete Outcome Data	Low risk	Study is free of missing outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	High risk	Very small sample sizes (Cases, n=3; Controls, n=6)
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

Table S31. Risk of bias assessment for Shafik (2014)

Domain	Rating	Justification
Recruitment	Low risk	Study lacks a complete description of recruitment methods, but otherwise no reason to suspect there were substantial differences between comparison groups other than uranium exposure.
Blinding	Low risk	Urine samples for uranium concentration analysis were re-coded to ensure blinding of key personnel.
Exposure Assessment	Low risk	The method for monitoring uranium concentration in urine samples (KPA) is robust.
Confounding	High risk	Cases represented and older cohort than controls.
Incomplete Outcome Data	Low risk	Study was free of missing outcome data.
Selective Reporting	Not applicable	In this case-control study, cases were selected on the basis of outcome, thus selective outcome reporting is not capable of introducing risk of bias in the study.
Other Bias	High risk	Very small sample size (Controls, n=5). No statistical test of difference in uranium concentrations was performed.
Conflict of Interest	Probably low risk	Associated funds and persons appear to be from academia only and free of financial interests in study results. However, no claim denying conflicts of interest was made.

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