Casual Friday Series

Heavy-Hitting Heavy Metals
Arsenic

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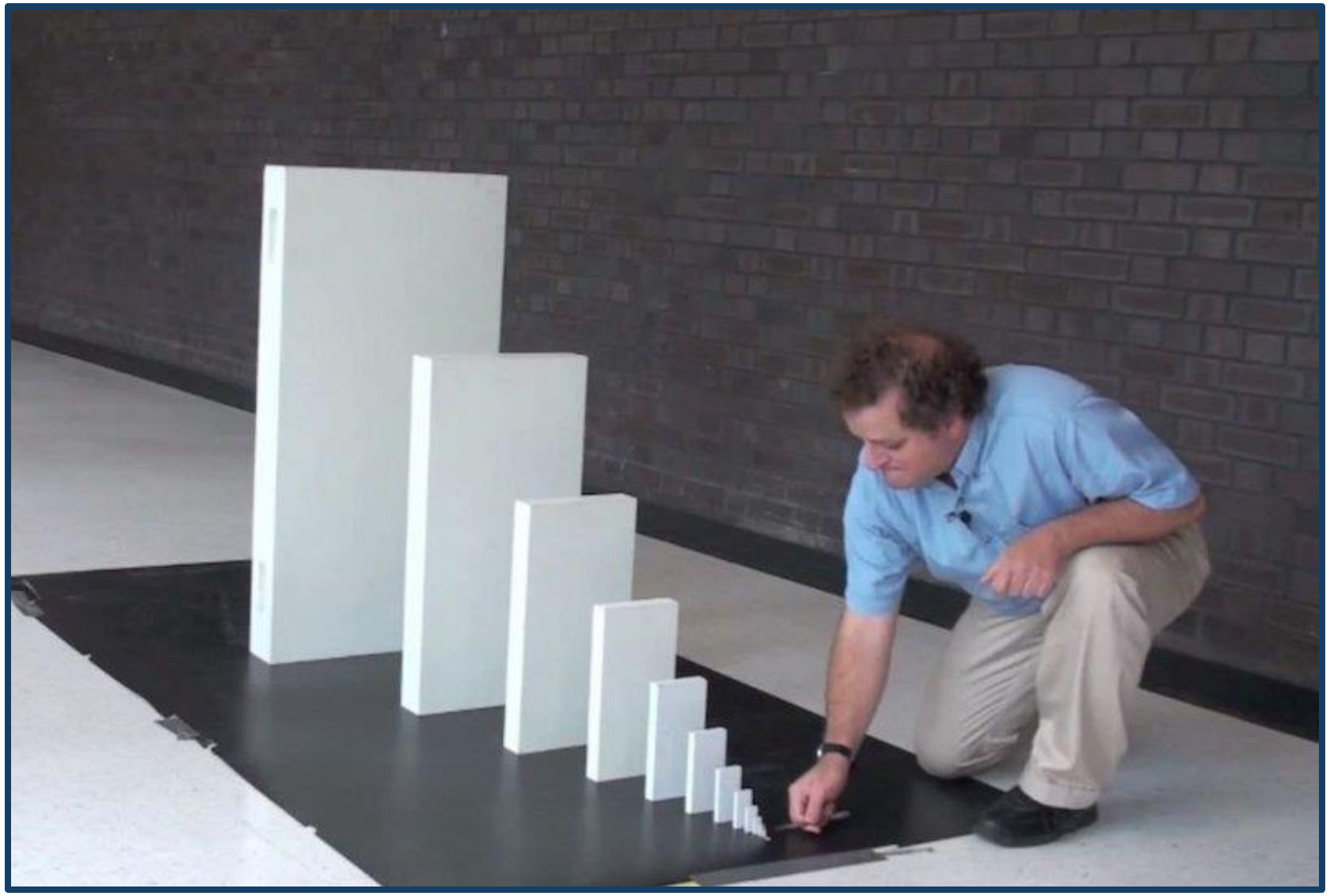

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Arsenic Exposure and Cardiovascular Disease: An Updated Systematic Review

Katherine Moon [1], Eliseo Guallar [2,3,4], Ana Navas-Acien [1,2]

Inorganic arsenic is a naturally occurring toxic metalloid found primarily in drinking water and food [1–3], with an estimated 100 million people worldwide exposed to arsenic at levels exceeding 50 µg/L [4, 5]. In epidemiologic studies, high-chronic arsenic exposure has been linked to cardiovascular disease (CVD), including coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD) [6, 7]. In particular, arsenic has been established as a cause of blackfoot disease, a form of PAD endemic to areas of Taiwan with extremely high levels of arsenic in drinking water [4, 8, 9]. Experimentally, arsenic exposure can induce atherogenesis and endothelial dysfunction in animal models [10–17]. Proposed mechanisms include up-regulation of inflammatory signals, enhanced oxidative stress, endothelial and smooth muscle cell proliferation, vessel remodeling, and apoptosis [10–12, 16, 17].

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Most studies assessed arsenic exposure using indirect measures (e.g., living in high arsenic areas) [34, 37, 42, 44] or using environmental measures, such as arsenic in drinking water at the region/county/zip code/municipal/village level [24, 27, 31•, 32•, 36], at the household/individual level [28••, 29•, 30, 33, 38, 41], or in air [43]. Two of the studies measuring arsenic in drinking water calculated an arsenic exposure index accounting for duration of water consumption [24, 27]. Few studies measured biomarkers of arsenic exposure such as urine [24, 28••, 35, 40] or hair [39].

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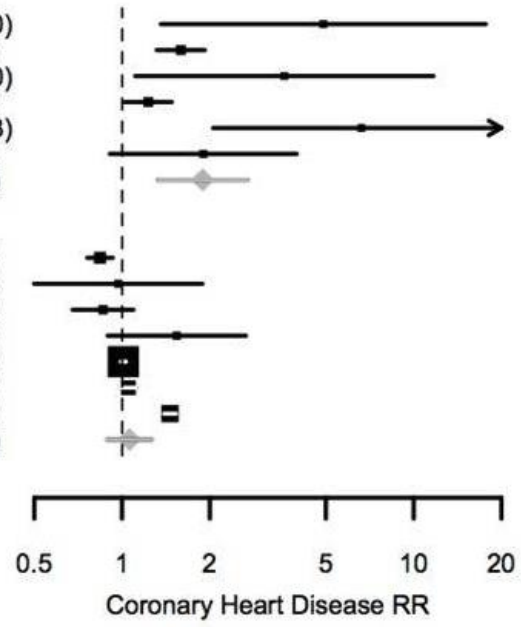
Study	Cases/Controls	Marker	Exposure Group	Reference Group	RR (95% CI)
High Exposure Areas					
Chen et al. 1996	39/2,517	Water	>20.0 mg/L-y	0 mg/L-y	4.90 (1.36, 17.70)
Tsai et al. 1999	728 deaths	Water	Exposed region	Unexposed region	1.59 (1.32, 1.93)
Tseng et al. 2003	78/384	Water	≥15.0 mg/L-y	0 mg/L-y	3.60 (1.11, 11.70)
Yuan et al. 2007	2,196 deaths	Water	Exposed region	Unexposed region	1.22 (1.02, 1.47)
Afridi et al. 2011	58/61	Urine	6.06 µg/L	3.66 µg/L	6.62 (2.05, 21.33)
Chen et al. 2011	34 deaths	Urine	351.9-1,100 µg/g creatinine	6.6-105.9 µg/g creatinine	1.90 (0.91, 3.98)
				Pooled RR:	**1.89 (1.33, 2.69)**
Low-Moderate Exposure Areas					
Engel & Smith 1994	63,831/~1.7 million	Water	>20 µg/L	5-10 µg/L	0.84 (0.76, 0.93)
Ruiz-Navarro et al. 1998	29/49	Urine	75th percentile	25th percentile	0.97 (0.50, 1.89)
Lewis et al. 1999	411/3,647	Water	≥5 mg/L-y	<1 mg/L-y	0.86 (0.68, 1.10)
Zierold et al. 2004	128/1,057	Water	>10 µg/L	<2 µg/L	1.54 (0.90, 2.68)
Meliker et al. 2007	26,646 deaths	Water	Exposed counties	General population	1.01 (0.99, 1.03)
Medrano et al. 2010	50,244 deaths	Water	>10 µg/L	<1 µg/L	1.05 (0.96, 1.08)
Gong & O'Bryant 2012	69/430	Water	8.1 µg/L	4.1 µg/L	1.46 (1.39, 1.53)
				Pooled RR:	**1.06 (0.89, 1.26)**



*RR Relative Risk for CHD

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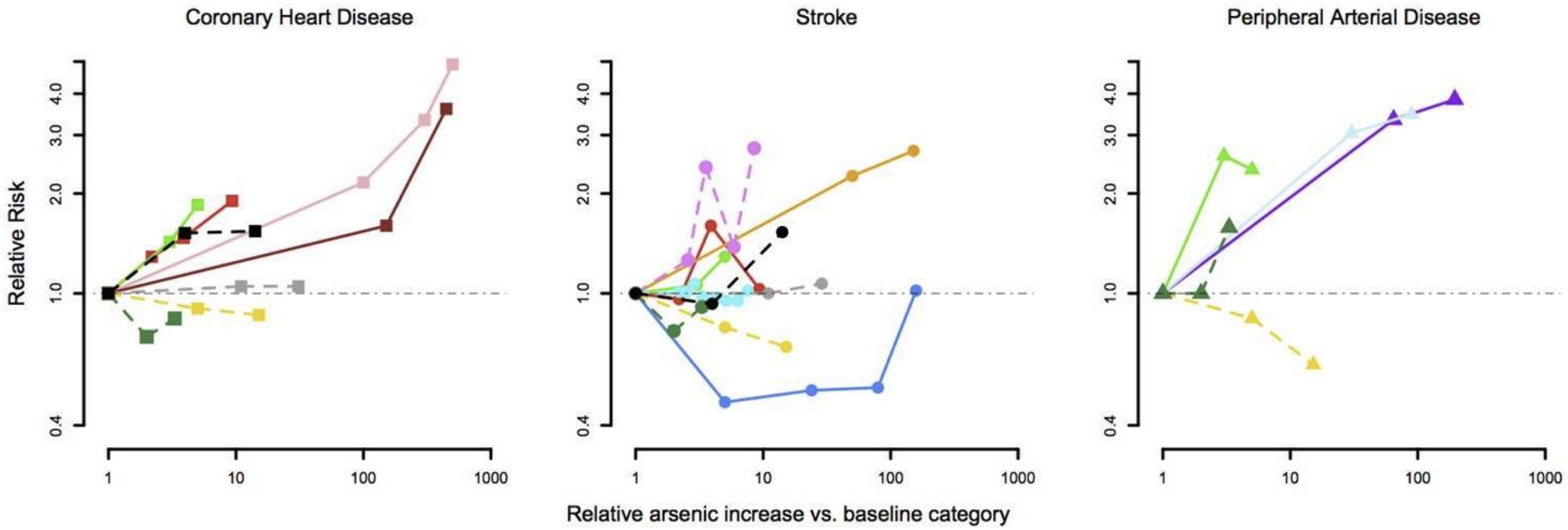

Among nine studies (four in the updated search and five from the previous review) conducted in high arsenic exposure areas that reported three or more exposure categories, two of three found a consistent dose-response trend for CVD [29•, 30] (data not shown) and all four found a consistent dose-response trend for CHD [23, 28••, 56, 58] (Figure 2). For stroke, three of four studies in high exposure areas [30, 57, 58] found that risk of stroke increased with increasing arsenic levels (Figure 2). For PAD, two of three studies in high exposure areas found a dose-response trend [24, 55] (Figure 2).

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The consistency of the associations across different populations, the availability of prospective studies, the clear dose-response relationships, and the decrease in CVD mortality following arsenic reduction [18, 19, 37] all support that the association between high-dose arsenic exposure and CVD is causal. Experimental and mechanistic evidence, including enhanced oxidant signaling and vessel remodeling, provide additional support for a role of high-chronic arsenic exposure in CVD of atherosclerotic origin [10–12, 16, 17]. Overall, we conclude that current evidence is sufficient to infer a causal relationship between high-chronic arsenic exposure and CVD, although future studies with improved exposure and outcome assessment should provide a more complete picture of the burden of arsenic-induced CVD in high exposure areas.

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Arsenic Exposure through Dietary Intake and Associated Health Hazards in the Middle East

Dietary arsenic (As) contamination is a major public health issue. In the Middle East, the food supply relies primarily on the import of food commodities. Among different age groups the main source of As exposure is grains and grain-based food products, particularly rice and rice-based dietary products. Rice and rice products are a rich source of core macronutrients and act as a chief energy source across the world. The rate of rice consumption ranges from 250 to 650 g per day per person in South East Asian countries. The source of carbohydrates through rice is one of the leading causes of human As exposure. The Gulf population consumes primarily rice and ready-to-eat cereals as a large proportion of their meals. Exposure to arsenic leads to an increased risk of non-communicable diseases such as dysbiosis, obesity, metabolic syndrome, diabetes, chronic kidney disease, chronic heart disease, cancer, and maternal and fetal complications. The impact of arsenic-containing food items and their exposure on health outcomes are different among different age groups. In the Middle East countries, neurological deficit disorder (NDD) and autism spectrum disorder (ASD) cases are alarming issues. Arsenic exposure might be a causative factor that should be assessed by screening the population and regulatory bodies rechecking the limits of As among all age groups. Our goals for this review are to outline the source and distribution of

chain. Arsenic exposure in nearly 1 billion of the population is through food and >200 million of the population through drinking water beyond the exposure limit of 10 µg/L [70]. As toxicities through food depend on food choice, culture, age group, and dietary restrictions. The consumption of a single food throughout the year without seasonal variety might be a worsening factor of toxic exposure. The ingestion of As through rice and legumes is considered a public health problem [3]. Rice has the highest capacity to absorb arsenic as compared to other cereal grains such as barley, wheat, oat, rye, and corn. Risk assessment was analyzed by the EFSA [71]. The European population concluded that cereals and processed foods are the primary cause of iAs exposure in the population, while water, rice, and dairy products exhibit a major role in iAs exposure in infants and toddlers. Other seafood and beverages such as apple juice have also been considered as a source of iAs toxic exposure. Lynch et al. (2014) estimated mean values in four different food groups, including seaweed/algae at 11,000 µg/kg, seafood at 130 µg/kg, rice at 130 µg/kg, and other cereal-related products at 92 µg/kg [72]. Arsenate (iAsV) or arsenite (iAsIII) are inorganic forms of arsenic present in food and drinking water—after ingestion, iAsV is converted to iAsIII—whereas seafood contains organic forms of arsenic, arsenobetaine and arsenocholine [7]. Root vegetables accumulate the highest As content and the lowest edible parts [73]. As contamination in various types of food and beverages in combination plays a major role in the progression of dangerous diseases such as cancer. Cancer has turned out to be an alarming public health concern for the whole world [74,75,76,77]. Consequently, the EFSA and JECFA reported a benchmark dose level (BMDL): 0.3–8 mg/kg body weight per day can be the cause of various kinds of cancer such as lung, skin, and bladder cancers.

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iAs present in the human body is generally excreted through urine and bile [78]. Urinary arsenic measurements (iAs%, MMA%, and DMA%) act as indicators of arsenic metabolism and methylation capacity [79,80]. Trans-cellular and paracellular pathways are major modes of iAs transportation [81]. Cellular metabolism includes methylation in four forms, namely monomethylarsonic acid (MMA^{V}), monomethylarsonous acid (MMA^{III}), dimethylarsinic acid (DMA^{V}), and dimethylarsinous acid (DMA^{III}). Among the different forms, MMA^{III} is reported as the most cytotoxic [82]. MMA^{III} species can inhibit mitochondrial I and III processes by electron escape through the electron transport chain, leading to the production of reactive oxygen species (ROS) and reactive nitrogen (RNS). Free radical production leads to DNA damage and impaired gene expression [83]. Enzymatic methylation occurs by way of the primary enzyme involved in As metabolism, called arsenic (3+) methyltransferase (AS3MT), and endogenous reducing agents such as thioredoxin (Trx) and glutathione (GSH) [84,85].

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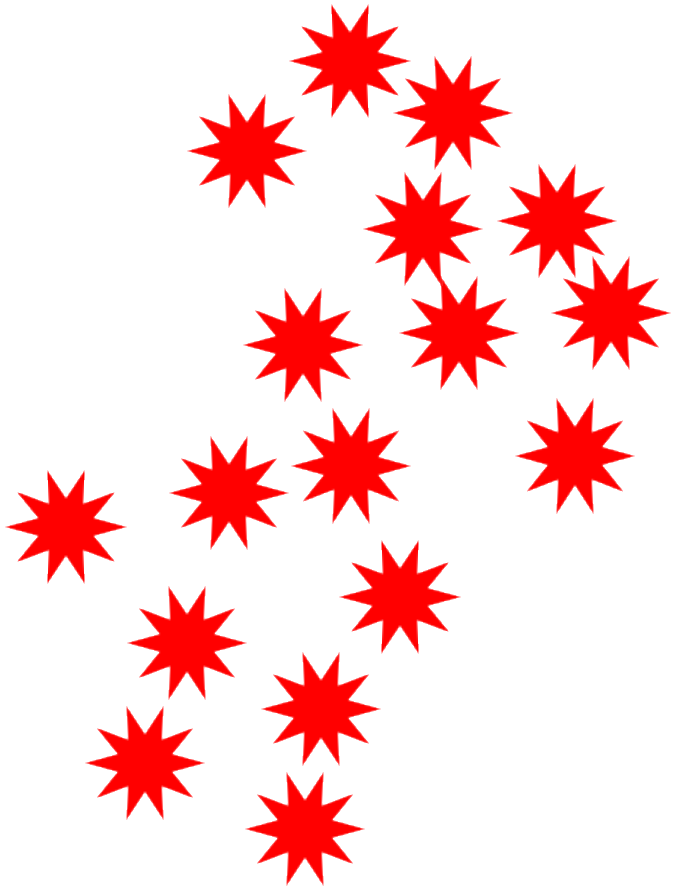
negative feedback mechanisms during glycolysis. Arsenic inhibits the conversion of pyruvate to acetyl coenzyme A (acetyl-coA), which leads to diminished cellular glucose uptake, gluconeogenesis, the oxidation of fatty acid, and further acetyl-CoA production. Mitochondria is an important cellular target by arsenite and free radical production, lipid peroxidation, H_2O_2 production, and mitochondrial swelling. Arsenic induces the formation of superoxide anion radicals such as singlet oxygen, the peroxyl radical, hydroxyl radicals, NO, H_2O_2, dimethyl-arsinic-peroxyl radicals, and dimethylarsinic radicals in a dose-dependent manner and consequently leads to health complications [88].

= Glucose Molecule



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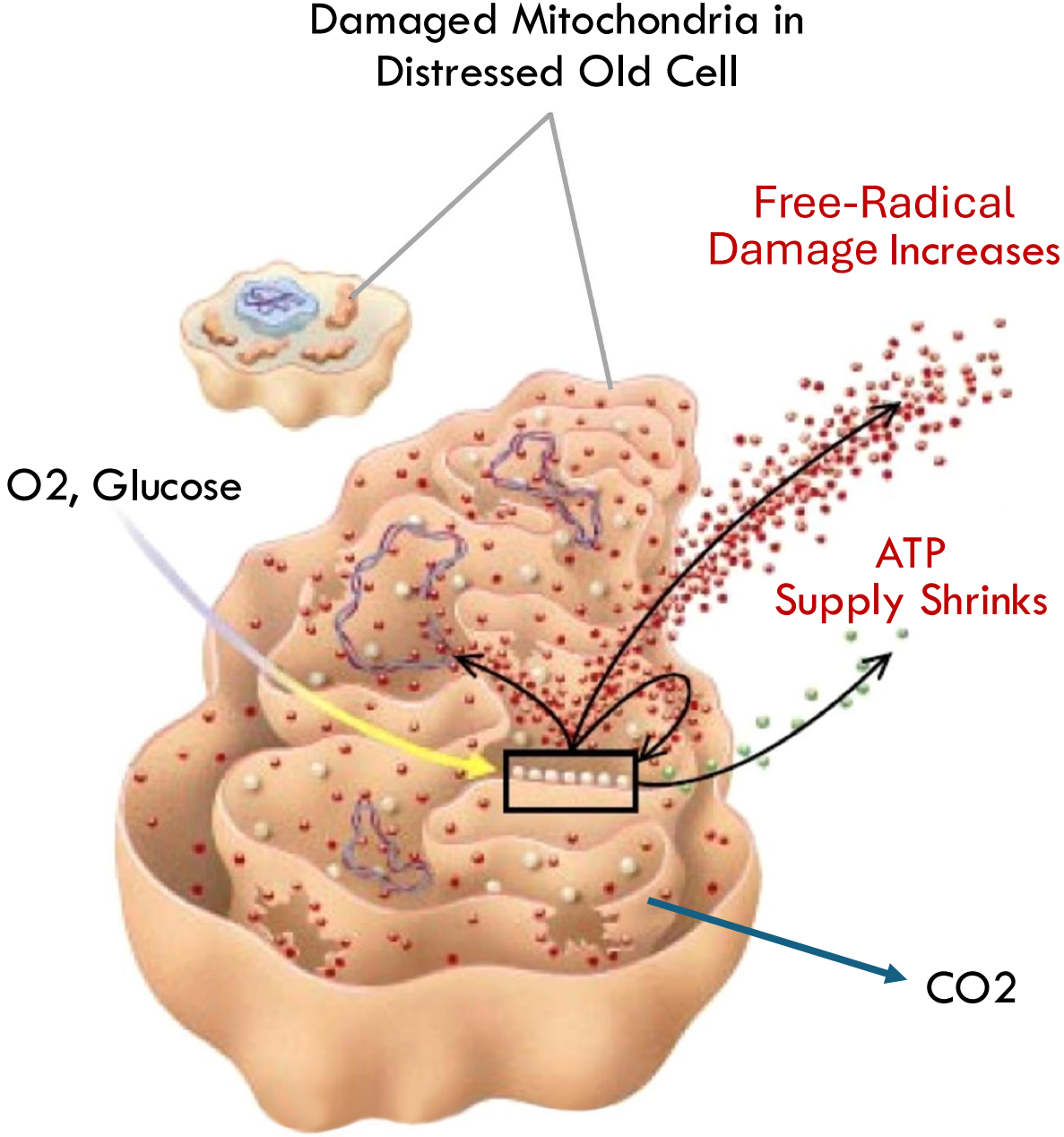
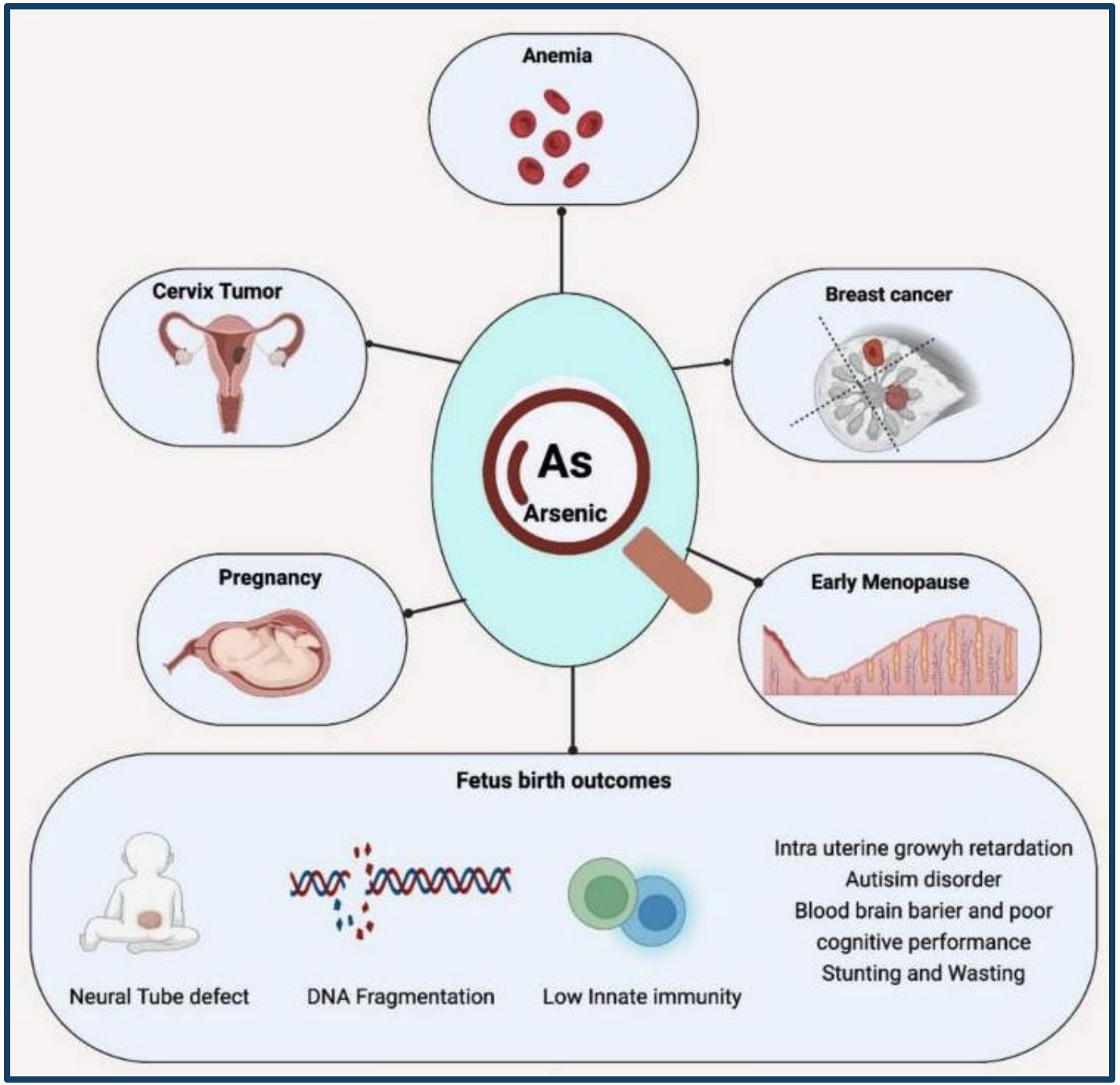


Table 4.

Various arsenic species and associated health hazards.

Arsenic Chemical Forms	Health Effects	References
Inorganic arsenic (As^{III} and As^{V})	Cancer	[100]
	Chronic diseases	[101,102]
	Mutation	[103]
	DNA damage	[104]
	Mitochondrial dysfunction	[105]
	Reduces bone mineralization	[106]
	Hyperglycemia	[107]
	Lipid disorders	[108]
	Coronary heart disease	[109]
	Liver toxicity	[110]
	Hypertension	[111]
	Genotoxicity	[112]
Arsenite (As^{III})	Cancer	[113]
	Fatty liver	[114]
	Hepatotoxicity	[115]
Arsenic trioxide	Breast cancer	[116]



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There are different toxic levels of iAs that have been identified in various samples such as scalp hair arsenic (1.0 < 3.0 mg/kg), toenail arsenic (>0.5 µg/g), total organic blood arsenic (>130 nmol/L), urinary arsenic (>100 µg/L), and spot urine sample arsenic (>50 µg/L), considered as upper abnormal limits [175]. An oral intake of 100–300 mg (1–5 mg/kg BW) of iAs in humans usually leads to death within 1 h, if untreated [175,176].

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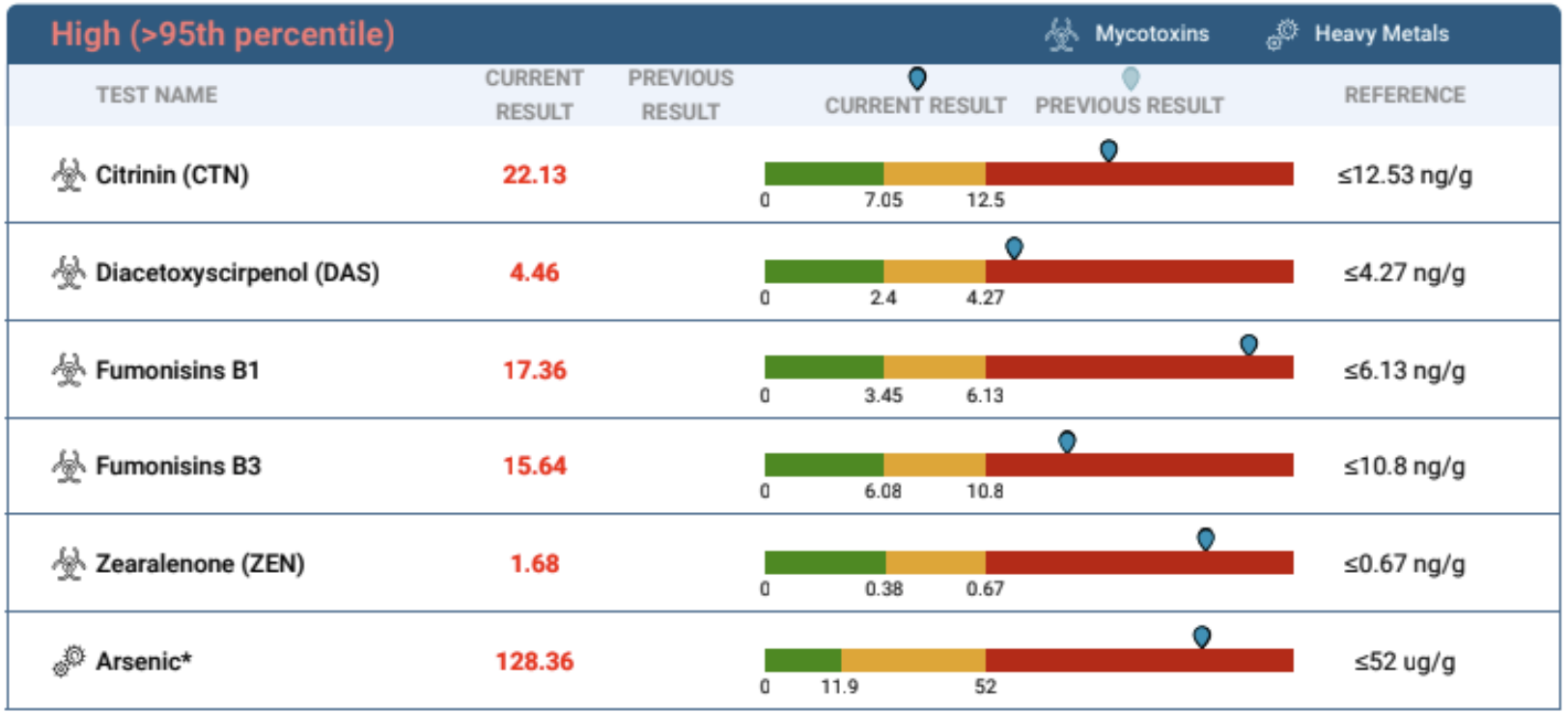

57 yo female, DM2

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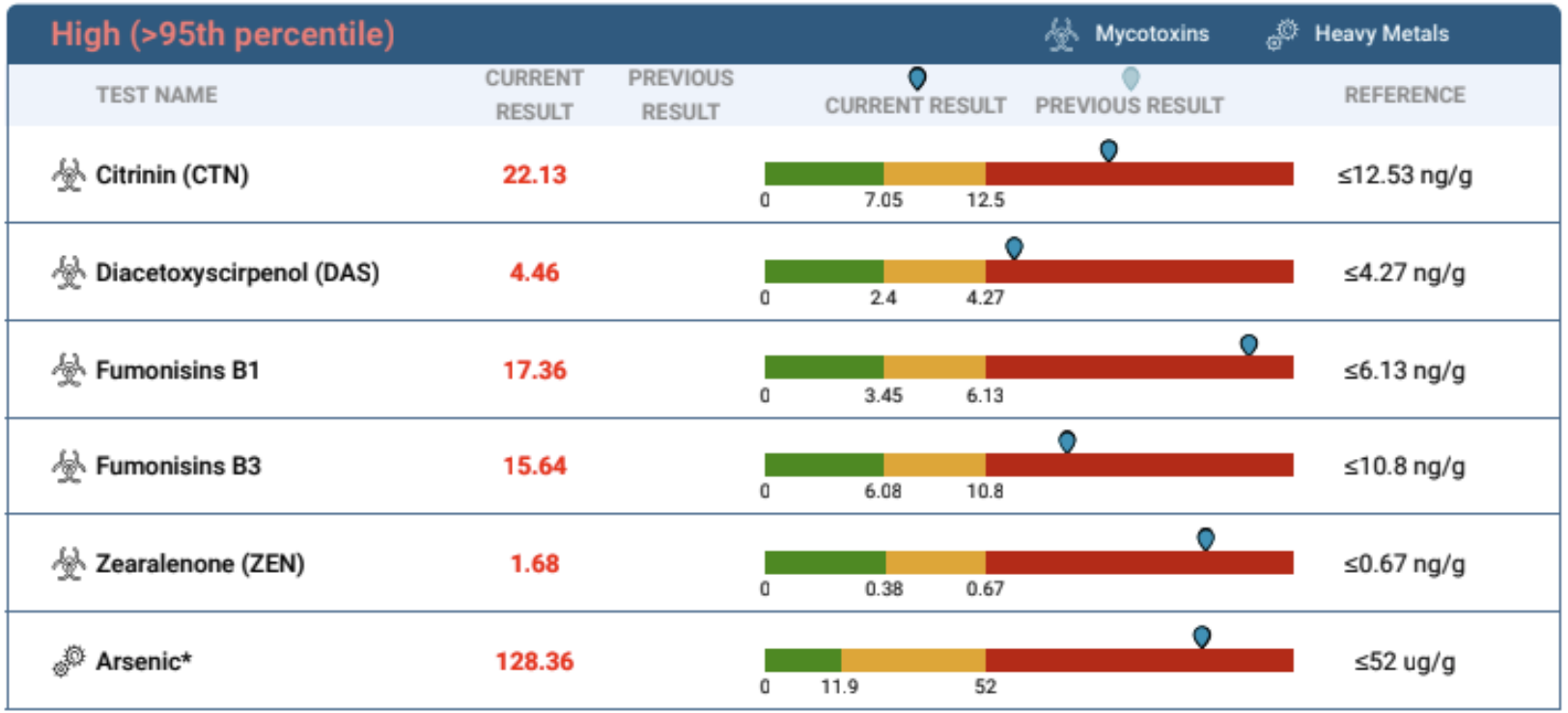

Sample Calculation:

2g of creatinine/L urine
128.36 ug/g of creatinine
= 256.72 ug/L urine

*Study Suggestion: <100ug/L urine

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67 yo female, Hypothyroidism, DM2, Hyper-lipidemia, elevated CRP, excess body wt

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Sample Calculation:

2g of creatinine/L urine
169.74ug/g of creatinine
= 339.48 ug/L urine

*Study Suggestion: <100ug/L urine

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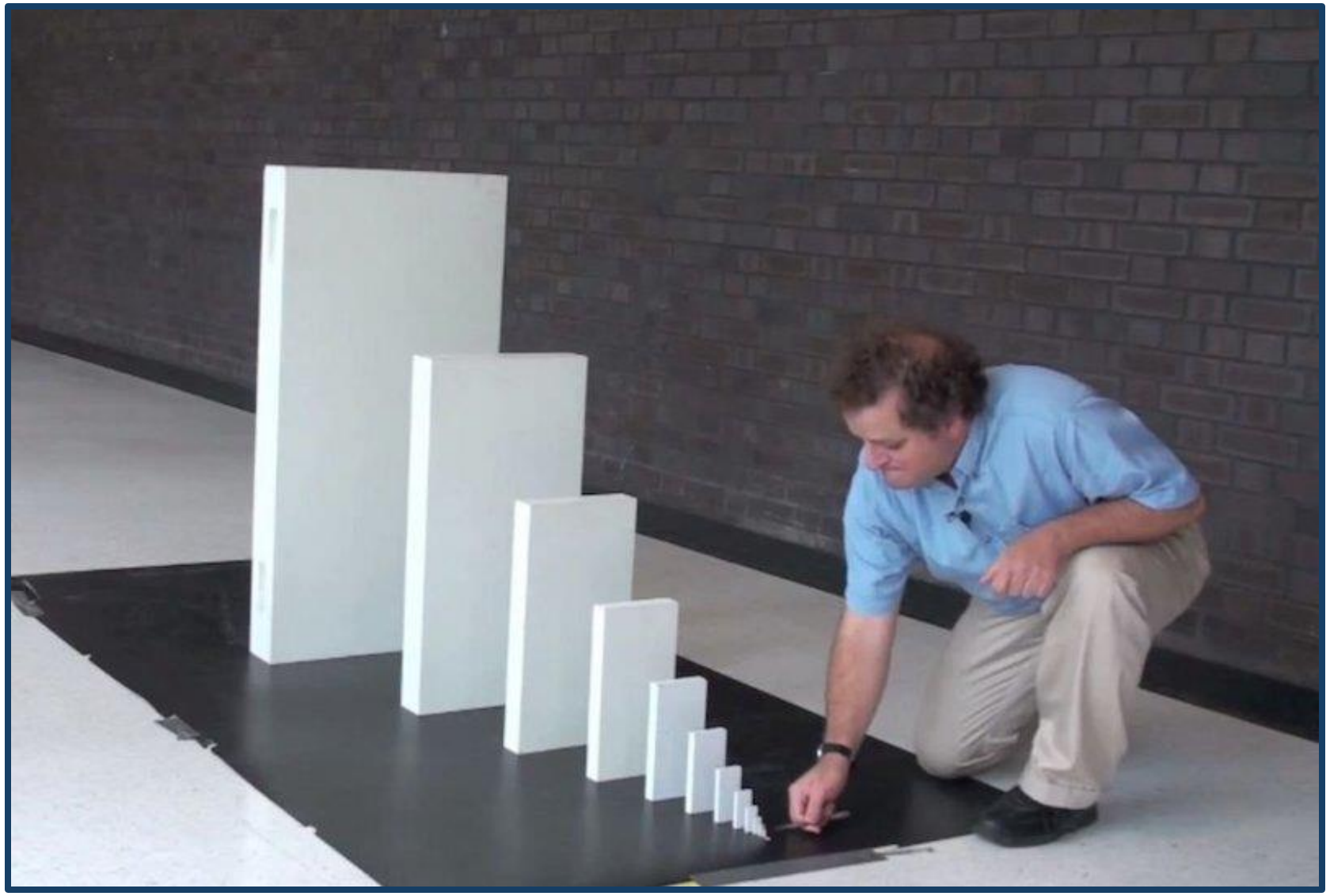

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