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Commentary

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"Commentary: Salivary N1-Methyl-2-Pyridone-5-Carboxamide, a Biomarker for Uranium Uptake, in Kuwaiti Children Exhibiting Exceptional Weight Gain"

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A recent longitudinal study published in Frontiers in Endocrinology has conducted salivary metabolomics analyses in 94 Kuwaiti children, out of which 51 became obese and metabolic syndrome positive after the first 2 years, i.e. 2011-2012 [1]. In the second phase of this study (2013-2014), the authors selected Kuwaiti children 10 years of age and probably using the same cohort. The authors have very appropriately stated that lifestyle disorders such as obesity, hypertension, and type 2 diabetes are prevalent in Kuwait. Previously, these disorders were suggested to be linked to diet, lack of physical activity, and sleep behavior [2]. Alqaderi et al. developed a linear regression [2], mixed-effect model with waist circumference as the outcome that showed a significant correlation with bedtime, salivary glucose, systolic blood pressure, and ethnicity with the exception of those children of Persian origin.

The communication of Goodson et al. has stated: "In the current study, we bring together data suggesting that uranium consumption may have contributed to the development of obesity in Kuwait children" [1]. The authors have reported the presence of N1-Methyl-2-Pyridone-5-Carboxamide (NMPC) in the saliva of all the children they tested both in the USA and Kuwait, probably because NMPC is one of the major metabolites of nicotinamide and nicotinate, two commonly consumed vitamins present in meat, fish, nuts, and mushrooms. The elevated levels reported among the obese Kuwaiti children is most logically linked to their dietary and possibly to their sleep behavior and lack of physical activity as the authors appropriately stated in their previous communication of 2017 [2].

The recent communication from Goodson et al. highlights the Menke et al. exploratory study associating higher levels of urinary uranium with diabetes but not insulin resistance. However, the comment by Wong et al. very appropriately noted paying "attention to the confounders when interpreting data by relying on urinary metal levels as a proxy for environmental exposure to examine potential association with overt diabetes [1,3,4]; specifically, it has previously been shown that subtle changes in renal physiology, as well as change in insulin and glucose levels, result in renal excretion rates of cadmium and other metals". Goodson et al. have indicated NMPC as a biomarker for uranium uptake in Kuwaiti children, based on the Grison et al. metabolomics study on effects of low-dose (40 mg L^{-1}) chronic exposure of uranium in rats over 9 months [1,5], proving the robustness of the metabolomic approach in detecting low level exposures and assessing the minimal dose required to detect a measurable biological effect of uranium contamination. However, Grison et al. were very cautious in suggesting that 11 features identified are not sufficient to build diagnostic tests because this requires identifying and quantifying the metabolites [5]. NPMC urinary concentration increases with contamination and is an indicator of an early renal disorder that might lead to morbidity. These authors also suggested a continuation of the work with additional experimental studies by testing additional biological matrixes thereby validating the non-linear dose-effect response observed in urine, and to examine major confounding factors. They were cautious in implying that their results provide some explanation with regards to the biological mechanisms triggered by low dose uranium exposure and risk to organ function, unlike the paper of Goodson et al. that characterized salivary NMPC as a uranium biomarker without any supporting data [1]. It would be prudent at this stage to highlight the fact that toxicity of a metal depends on several factors including sex, age, body mass index [6], and species. Humans are suggested to be the least sensitive mammal to uranium compared to other mammals in the following interspecies order: rabbit > rat > guinea pig > pig > mouse > dog > cat > human [7,8].

Goodson et al. articulated their study as bringing "together data suggesting that uranium consumption may have contributed to the development of obesity in Kuwait children" without substantiating this claim with data on natural uranium or depleted uranium in the samples [1]. However, it is completely unreasonable to relate levels of 238U in soil with salivary levels of NPMC without assessing the ingestion and inhalation routes and risks.

A comprehensive assessment of the uranium level in different environmental matrixes has been carried out by researchers at the Kuwait Institute for Scientific Research. The concentration ranges of ^{238}U and ^{234}U in seawater were 0.047-0.050, and 0.054-0.057 Bq l^{-1}, respectively [9]. The average ratio for $^{234}U/^{238}U$ in all the samples was greater than unity when secular equilibrium is attained. The most recent monitoring of the $^{234}U/^{238}U$ ratio in 10 large-volume seawater samples from Kuwait Bay was comparable to the previously reported results (1.06 ± 0.17) [9,10]. The concentration of ^{238}U, ^{235}U, ^{234}U in marine sediment varied between 22.3-30.5, 0.99-1.33, and 25.6-34.8 Bq kg^{-1} dry, respectively [11], and are well within the ranges which have been reported globally [12]. The 238U concentrations in terrestrial soils in 2002 at the contaminated site in Al-Doha varied between 14.6 and 87.0 Bq kg^{-1} dry [13]. However, the concentration from the adjacent area in clean soil was 13.5 ± 0.27 Bq kg^{-1} dry. Hence, the presumption of the Asimah Governorate having 15-20 Bq kg^{-1} higher ^{238}U activity is unsubstantiated by the environmental data. Considering the reported ^{238}U concentrations in soil in the Asimah Governorate, the dose from ingestion of soil using ICRP 119 parameters would be 1.66 nSv y^{-1}, a value that is several orders of magnitude lower than the UNSCEAR reported values for Public exposure to natural radiation from ingestion average value of 0.29 mSv [12,14].

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In addition to the marine samples; the concentration of uranium isotopes in aerosols were below the detection limit (2.5 μBq/m^3) at six locations sampled during the year 2018 [15]. The annual committed effective dose due to inhalation associated with such low concentrations was calculated for adults and children as 21 and 18 nSv, respectively, which are insignificant compared to the UNSCEAR reported values of Public exposure to natural radiation from total inhalation dose (1.26 mSV) [12].

The argument and assumption of Goodson et al. that uranium consumption may have contributed to the development of obesity in Kuwaiti children call for reconsideration since the baseline data for uranium does not support an increase in dose contribution via inhalation and/or ingestion pathways [1]. In addition to our observations, the IAEA report cited by Goodson et al. explicitly states that DU does not pose a radiological hazard to the population in Kuwait [1,13], and underscores that no remedial measures are necessary at any of the investigated sites, with the exception of DU stored at the Um Al-Kwaty military base. To set the record straight, that site has been remediated and the military base closed in 2005. Hence, associating obesity among Kuwaiti children to a higher uranium dose in the Asimah Governorate remains a counterfactual assumption unsubstantiated with local environmental uranium data.

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