Peter A. Ricketti, DO[*]
David W. Unkle, MSN, APN, FCCM[†]
Dennis J. Cleri, MD, FACP, FAAM, FIDSA[‡]
Anthony J. Ricketti, MD, FACAI[‡]
[*]*Department of Internal Medicine*
University of Medicine & Dentistry of New Jersey
New Jersey Medical School
Newark, New Jersey
[†]*Department of Family Medicine*
University of Medicine & Dentistry of New Jersey
School of Osteopathic Medicine
Stratford, New Jersey
[‡]*Department of Medicine*
Seton Hall University School of Graduate Medical Education
South Orange, New Jersey
aricketti1@aol.com

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Association of urinary arsenic, heavy metal, and phthalate concentrations with food allergy in adults: National Health and Nutrition Examination Survey, 2005-2006

Evidence of the link between environmental chemicals and food sensitization or allergy is limited, although some recent studies have found that urinary triclosan, parabens, and dichlorophenol-containing pesticides but not bisphenols are associated with food sensitization.[1,2] The understanding of the possible role of environmental exposure in food sensitization is not complete. Therefore, it was aimed to study associations between other sets of urinary environmental chemical concentrations (including heavy metals, arsenic, and phthalates) and serum food specific IgE antibodies (including serum peanut, egg, milk, and shrimp IgE antibodies) in adults in a national and population-based setting.

As previously reported elsewhere,[3] the US National Health and Nutrition Examination Survey (NHANES) is a national, population-based, multiyear, cross-sectional study. Information on demographics, lifestyle factors, and health conditions was obtained by household interview using questionnaires. Written informed consent was obtained for all participants. In the 2005-2006 cohort, serum IgE concentrations were measured in people 1 year and older using the ImmunoCAP 1000 System (Pharmacia Diagnostics, Kalamazoo, Michigan). Urine samples were collected in selected people (approximately 20%-30% of the whole cohort, still representative) to measure environmental chemical concentrations. Urine specimens were processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia. Urinary environmental chemical concentrations are determined by inductively coupled plasma dynamic reaction cell mass spectroscopy or detected using online solid-phase extraction, isotope dilution, and high-performance liquid chromatography separation, followed by electrospray ionization and tandem mass spectrometry on those 6 years and older.[4–6] In the current study, urinary environmental chemical concentrations included heavy metals, arsenic, and phthalates. Because urinary environmental chemical concentrations were highly skewed, they were all log transformed in the analyses.

For food sensitization identification, a clinical cutoff of 0.35 kU/L was used.[1,7] For food allergy identification, thresholds were set at 14 kU/L for peanut IgE antibody, 7 kU/L for egg IgE antibody, 15 kU/L for milk IgE antibody, and 5 kU/L for shrimp IgE antibody according to the recent literature.[8] In the present study, study participants 20 years and older were included (N = 4,979). Covariates, including age, sex, ethnicity, ever having asthma, and urine creatinine level, were adjusted. Effects of all included urinary environmental chemical concentrations on food sensitization or allergy were both examined by logistic regression models, with $P < .05$ considered statistically significant. In addition, all the analyses were weighted for the survey design. Stata statistical software, version 13.0 (Stata Corp, College Station, Texas), was used to perform all the analyses. Because this study is

Table 1
Associations between urinary arsenic and heavy metal concentrations and food sensitization in adults

Food sensitization	Peanut (n = 360 [7.2%])		Egg (n = 130 [2.6%])		Milk (n = 166 [3.3%])		Shrimp (n = 320 [6.4%])	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Total arsenic	1.16 (0.92-1.47)	.19	1.20 (0.92-1.55)	.16	0.94 (0.72-1.23)	.62	1.12 (0.91-1.38)	.25
Arsenous acid	2.22 (1.04-4.75)	.04	1.10 (0.13-9.09)	.92	0.69 (0.05-9.06)	.76	1.76 (0.59-5.32)	.30
Arsenic acid	1.94 (0.83-4.54)	.12	2.50 (0.83-7.48)	.10	1.68 (0.57-4.95)	.32	1.97 (1.07-3.63)	.03
Arsenobetaine	1.11 (0.94-1.32)	.20	1.06 (0.83-1.35)	.60	0.97 (0.81-1.17)	.73	1.00 (0.83-1.21)	.98
Arsenocholine	1.10 (0.44-2.72)	.83	0.12 (0.004-3.48)	.20	0.76 (0.12-4.99)	.76	0.70 (0.19-2.65)	.58
Dimethylarsonic acid	1.18 (0.83-1.66)	.34	1.33 (0.89-1.98)	.15	0.78 (0.46-1.29)	.31	1.23 (0.90-1.67)	.18
Monomethylarsonic acid	1.40 (0.86-2.26)	.16	1.68 (0.89-3.11)	.10	0.81 (0.33-1.97)	.62	1.44 (1.00-2.07)	.051
Trimethylarsine oxide	NA	NA	NA	NA	NA	NA	0.99 (0.83-1.17)	.89

Abbreviations: CI, confidence interval; NA, not applicable.

Disclosures: Author has nothing to disclose.

Table 2
Associations between urinary arsenic and heavy metal concentrations and food allergy in adults

Food allergy	Peanut (n = 8 [0.2%])		Egg (n = 1 [0.2%])		Milk (n = 1 [0.2%])		Shrimp (n = 21 [0.5%])	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Arsenous acid	2.19 (0.29-16.46)	.42	NA	NA	NA	NA	2.04 (0.22-19.20)	.51
Arsenic acid	NA	NA	NA	NA	21.03 (1.94-227.70)	.02	4.04 (1.72-9.49)	.003
Arsenobetaine	1.80 (0.18-18.07)	.60	NA	NA	NA	NA	1.81 (0.71-4.58)	.20
Arsenocholine	NA	NA	NA	NA	NA	NA	2.49 (0.79-7.86)	.11
Dimethylarsonic acid	4.79 (0.52-44.31)	.15	1.61 (0.82-3.14)	.15	0.56 (0.42-0.75)	.001	4.68 (1.28-17.11)	.02
Monomethylarsonic acid	2.98 (1.03-8.63)	.04	NA	NA	NA	NA	3.86 (1.04-14.33)	.04
Trimethylarsine oxide	NA	NA	NA	NA	NA	NA	NA	NA
Mercury	3.42 (0.41-28.86)	.24	0.43 (0.26-0.71)	.002	1.31 (1.15-1.49)	<.001	1.22 (0.45-3.29)	.68
Barium	1.31 (0.23-7.41)	.74	1.10 (0.74-1.66)	.59	5.42 (3.16-9.29)	<.001	0.91 (0.71-1.16)	.41
Cadmium	4.50 (0.23-87.92)	.30	0.96 (0.55-1.69)	.88	10.61 (5.40-20.84)	<.001	1.48 (0.58-3.78)	.38
Cobalt	4.84 (0.40-58.06)	.20	2.23 (1.48-3.35)	.001	0.64 (0.51-0.80)	.001	0.98 (0.54-1.79)	.94
Cesium	17.66 (0.02-1375.23)	.37	214.30 (11.90-3859.77)	.001	1.15 (0.95-1.39)	.13	0.94 (0.67-1.33)	.71
Molybdenum	3.84 (0.08-187.85)	.47	2.61 (1.55-4.39)	.001	2.57 (2.15-3.07)	<.001	1.06 (0.56-2.2)	.84
Lead	1.81 (0.96-3.43)	.07	3.83 (2.30-6.39)	<.001	4.54 (3.35-6.16)	<.001	2.00 (1.00-4.00)	.049
Platinum	13.59 (0.33-565.64)	.16	1.15 (0.93-1.42)	.17	NA	NA	NA	NA
Antimony	2.83 (0.69-11.59)	.14	0.53 (0.25-1.13)	.09	2.52 (1.96-3.23)	<.001	0.50 (0.17-1.46)	.19
Thallium	5.84 (0.01-4863.65)	.58	1.95 (0.89-4.27)	.09	1.14 (0.92-1.41)	.22	1.54 (0.55-4.32)	.39
Tungsten	1.06 (0.57-1.99)	.84	1.12 (0.84-1.48)	.42	7.34 (3.40-15.84)	<.001	0.95 (0.59-1.54)	.83
Uranium	2.56 (0.70-9.38)	.14	0.78 (0.44-1.41)	.39	18.13 (3.41-96.31)	.002	1.76 (1.14-2.72)	.01

Abbreviations: CI, confidence interval; NA, not applicable.

a secondary data analysis by extracting data from the NHANES website, no further ethics approval is required.

Urinary arsenic concentrations were observed to be associated with food sensitization and/or allergies. For example, urinary arsenic acid and monomethylarsonic acid concentrations were both associated with shrimp sensitization (odds ratio [OR], 1.97; 95% confidence interval [CI], 1.07-3.63; $P = .03$; and OR, 1.44; 95% CI, 1.00-2.07; $P = .051$; respectively) and allergy (OR, 4.04; 95% CI, 1.72-9.49; $P = .003$; and OR, 3.86; 95% CI, 1.04-14.33; $P = .04$; respectively). They seem to be related to peanut sensitization and allergy as well (Table 1 and Table 2). A few chemicals, including mercury, cadmium, lead, molybdenum, antimony, tungsten, and possibly uranium, were associated with milk allergy. Notably, urinary lead concentrations were almost associated with all 4 included food allergy (peanut: OR, 1.81; 95% CI, 0.96-3.43; $P = .07$; egg: OR, 3.83; 95% CI, 2.30-6.39; $P < .001$; milk: OR, 4.54; 95% CI, 3.35-6.16; $P < .001$; shrimp: OR, 2.00; 95% CI, 1.00-4.00; $P = .049$). Among urinary phthalate concentrations (data now shown), only urinary mono-(2-ethyl)-hexyl phthalate, mono-benzyl phthalate, mono-(3-carboxypropyl) phthalate, mono-(2-ethyl-5-oxohexyl) phthalate, and mono-2-ethyl-5-carboxypentyl phthalate were found to be associated with shrimp allergy (OR, 2.79; 95% CI, 1.64-4.77; $P = .001$; OR, 1.74; 95% CI, 1.20-2.51; $P = .006$; OR, 1.45; 95% CI, 1.20-1.75; $P = .001$; OR, 2.92; 95% CI, 1.85-4.61; $P < .001$; and OR, 3.83; 95% CI, 2.27-6.45; $P < .001$; respectively).

In this national, population-based, cross-sectional study, it was observed that higher urinary arsenic, heavy metal, and phthalate concentrations were associated with food sensitization and allergies in adults in the United States. Specifically, shrimp and milk allergy were found to be related to many chemicals. Moreover, lead could also be the most notable chemical because its risk effect was apparent across all 4 included food allergies.

According to previous animal models, immunotoxicologic effects induced by concurrent exposure to arsenic were evident on the suppression of cellular and humoral immune responses.[9] The current study also provided human evidence that the effect has persisted in serum food specific IgE antibodies. A focus on the risk effect from arsenic in the general population should be noted hereafter. Elevated urinary cadmium levels could be coming from foods or cigarette smoke (including secondhand smoke). Increased cadmium levels could affect normal development and interfere with the effects and bioavailability of beneficial nutrients and also have negative effects on activities of a variety of cellular enzymes.[10] A previous human study[10] has reported that children with food allergy had higher cadmium levels. The present study has provided further evidence on the relationship with food allergy in adults. In addition to cadmium, risk effect of lead will also require further investigation to understand the mechanism.

It is known that phthalates are commonly found in foods and could have significant effects on human health. In the current analysis, it was observed that quite a few phthalate metabolites were associated with shrimp allergy. One would suspect that the canned seafood for family cooking could be the main source in the households. Still, the causality cannot be established because of its cross-sectional design in nature. Further clinical studies, including animal and human studies, on its toxicologic effects are suggested for confirmation on the link.

In summary, urinary arsenic, heavy metal, and phthalate concentrations were found to be associated with food allergy in adults. This study contains a large human study sample in a national representative setting. However, information on serum food specific IgE antibodies is still limited. Future research, including other food specific IgE antibodies (such as nuts, fish, and soy), is warranted. Studies with longitudinal design and/or clinical trials are needed to confirm or refute the observations. In practice, a possible phthalate source from canned seafood might need to be further regulated.

Ivy Shiue, PhD[*,†]
[*]*School of the Built Environment*
Heriot-Watt University
Edinburgh, Scotland, United Kingdom
[†]*Owens Institute for Behavioral*
Research University of Georgia
Athens, Georgia
ivy.shiue@ed-alumni.net

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Lack of allergenic soy in intralipid for total parenteral nutrition

The patient, a 36-year-old woman who was 29 weeks pregnant (gravida 1, para 0), presented with small bowel obstruction that required surgery. After surgery, the patient developed ileus and could not tolerate oral feeding. After consultation with a neonatologist, it was determined that the patient needed total parenteral nutrition (TPN) with lipids (intralipid soy parenteral nutrition) to support fetal growth. The nonlipid preparation of TPN does not supply essential fats or the total caloric requirements needed for fetal growth and development. Intralipid 20% (a 20% intravenous [IV] fat emulsion) contains 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection. The soybean oil is a refined natural product that consists of a mixture of neutral triglycerides of predominantly unsaturated fatty acids.

The patient had a history of severe itching and swelling of her mouth and throat immediately after ingesting soy products since childhood. The only lipid TPN that does not contain soy is Omegarin, which is not approved by the Food and Drug Administration (FDA). The FDA was contacted to obtain a compassionate-use waiver for the use of Omegarin; however, this was not granted. Because the lipid-containing TPN was considered essential for fetal growth and with the informed consent of the patient, a decision was made to desensitize the patient to the lipid-containing TPN product.

The patient was pretreated with antihistamines and transferred to the intensive care unit, where an anesthesiologist, obstetrician, and neonatologist were immediately available. Rapid IV desensitization was initiated using a protocol developed by Mariana Castells, MD, PhD, at Brigham and Women's Hospital in Boston, Massachusetts, for desensitization to chemotherapeutic agents and biological modifiers.[1] The patient was under continuous monitoring by an intensive care unit nurse and an allergist/immunologist, who evaluated the patient for signs and symptoms of an allergic reaction. Vital signs were obtained every 15 minutes.

The patient tolerated desensitization without reaction or change in vital signs. Blood samples obtained before desensitization, during desensitization, and after desensitization and a sample of the 20% IV fat emulsion were sent to Robert Hamilton, PhD, at Johns Hopkins Asthma and Allergy Center for analysis. Unfortunately, the blood samples from the patient were not properly handled at our institution. The level of IgE antibodies to soy in the patient's blood was 0.13 kUa/L, which is extremely low. Analysis of the 20% IV fat emulsion consisted of competitive inhibition in which 2 IgE antisoy serum samples were preincubated with the emulsion or buffer (sham control) for 2 hours. Both the buffer and the emulsion produced the same level of IgE antisoy antibodies, indicating no detectable soy allergen in the emulsion preparation. The patient's low specific IgE levels to soy suggest that she would not have developed symptoms even if the TPN product had contained soy.

This case leaves unanswered the question of whether another patient with high serum levels of IgE for soy could safely undergo IV desensitization to soy. Nevertheless, this case is important because (1) there is no previous report of attempted IV desensitization to a food product, (2) there is no previous report of attempted desensitization during pregnancy, and (3) it is important to recognize that labeled components of a product after processing and refinement may no longer be allergenic. The IV TPN supplement, although labeled as containing soy, does not in fact contain any allergenic soy. Because there was no detectable soy allergen in the 20% IV fat emulsion product, desensitization should not be necessary in patients who have a history of allergy to ingested soy and need to receive this product. This case also illustrates the need to consider the management of anaphylaxis in a pregnant patient,[2] which may require a coordinated effort among the allergist/immunologist, anesthesiologist, neonatologist, and the patient's obstetrician.

Richard A. Nicklas, MD
Department of Medicine
George Washington Medical Center
Washington, DC
rnicklas@mfa.gwu.edu

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Are skin tests useful in fluoroquinolone hypersensitivity diagnosis?

The incidence of adverse reactions to quinolones varies from 2% to 10%, but less than 2% of these reactions are mediated by an immunologic mechanism.[1] Quinolone allergy diagnosis is based on clinical history, skin prick test (SPT), intradermal test (IDT), and oral challenge.[2] The usefulness of skin tests (STs) is limited because false-negative and false-positive test results are common.[2,3] Quinolones can have an irritant effect, causing false-positive ST results, so there is still a lot of controversy about the appropriate concentration for quinolone skin testing and its usefulness.[3,4] On the other hand, the in vitro basophil activation test has undergone great

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