

Gastronomical Delight Micronutrients Protect against Arsenic Lesions

Studies in South Asia suggest that antioxidants may mediate many of the dermatologic symptoms associated with exposure to arsenic in drinking water. Nonetheless, the mitigating effects of diet on arsenic-related premalignant skin lesions are largely unknown, particularly in the context of the typical Bangladeshi diet. A new cross-sectional study using baseline data from the Health Effects of Arsenic Longitudinal Study (HEALS), 2000–2002, is the first systematic, population-based attempt to assess the association between micronutrient intake and the prevalence of arsenic-induced skin lesions [*EHP* 116:1056–1062; Zablotska et al.].



A diet rich in B vitamins and antioxidants may counter some of the effects of chronic arsenic ingestion

Tracking Down a Cause for Hypospadias Placental Malfunction May Contribute

Hypospadias is a male birth defect in which the opening of the urethra is located on the underside of the penis instead of the tip. Although the defect is common and increasing in prevalence (2–8 cases per 1,000 live births in Western countries), the causes of most cases are unknown. Some studies suggest that reduced levels of the placental hormone human chorionic gonadotropin (hCG) may play a role; others suggest associations between hypospadias and conditions such as low birth weight, preterm birth, and preeclampsia that could be caused by malfunction of the placenta and subsequent abnormalities in hormone regulation and nutrition provided to the fetus (a condition known as placental insufficiency). A new study now presents additional evidence that hypospadias has its origins in malfunction of the placenta [*EHP* 116:1071–1076; Akre et al.].

Data on 292 cases of hypospadias and 427 controls were collected as part of a joint Danish–Swedish study of both hypospadias and cryptorchidism (undescended testes). In Sweden, hypospadias cases were recruited at a pediatric surgery clinic, and data were collected via self-administered questionnaires. In Denmark, cases were from the Danish National Birth Cohort, a population-based cohort of women and children. Mothers were interviewed while pregnant and twice after delivery. Matched con-

As many as a third of the people living in Bangladesh have been exposed to arsenic-tainted water levels above the national limit of 50 ppb, with many levels as high as 800 ppb. Several studies have shown an association between drinking arsenic-rich water and development of skin lesions, a common outward sign of chronic arsenic exposure.

HEALS is a population-based prospective cohort study in Arai-hazar, Bangladesh, using individual-level time-weighted measures of arsenic exposure via drinking water. The present study relied on detailed daily diet information obtained from all participants using a food frequency questionnaire along with U.S. Department of Agriculture nutritional tables. The analyses were aimed at clarifying the effects of the B vitamin group and antioxidants (vitamins A, C, and E) on the risk of arsenic-related skin lesions. Because supplements and food fortification are rare in Bangladesh, only dietary intakes of these micronutrients were considered.

Skin lesions were identified among 10,628 subjects according to a structured clinical protocol during screening that was confirmed with further clinical review. Dietary intake of B₁, B₆, and B₉ and all three antioxidants significantly reduced the risk of arsenic-related skin lesions. For example, for individuals with the highest vitamin intake, the risk of arsenic-induced skin lesions was significantly reduced by 60% for vitamin E.

The investigators conclude that intakes of B vitamins and antioxidants at doses greater than the current recommended daily amounts for Bangladesh might lower the risk of arsenic-related skin lesions. However, the research team observed that there was a high prevalence of micronutrient deficiency in Bangladesh, with the potential protective modifying effects of these vitamins restricted to the medium and upper consumption levels. Public health measures to assist this population may need to include either supplementation or food fortification to achieve a significant degree of protection from chronic arsenic exposures. –M. Nathaniel Mead

controls were born within at least 6 months of each case and within the same county, and were randomly selected from national birth and population registries.

The investigators found several conditions independently associated with increased hypospadias risk, most of which they say could be explained by impaired production of hormones by the placenta. Mothers without first-trimester nausea were twice as likely to bear sons with hypospadias, as were mothers who had a prepregnancy body mass index of 30 or greater. These findings support the theory that placental insufficiency contributes to hypospadias. Nausea is believed to be caused by an early surge of pregnancy hormones, and the absence of first-trimester nausea is associated with low hCG levels. A previous study showed that obese women have lower levels of a family of proteins called plasminogen activator inhibitors, some of which are derived from the placenta.

The team also determined that a maternal diet lacking both fish and meat was associated with more than a fourfold increased risk of hypospadias in baby boys. This finding complements a 2000 study by other authors that showed a strong positive association between maternal vegetarian diet and hypospadias in offspring. The authors of the current study conclude that exclusion of animal proteins could increase the risk of a transient deficiency of some nutrient that's essential for formation of the organs or the placenta. Another explanation is that some protein sources in vegetarians' diets (such as soybeans) contain compounds with hormonal effects that may affect the development of the urogenital organs in humans. –Angela Spivey

Getting Straight on What's Flushed

"Sewage Epidemiology" Measures Community Drug Consumption

Active pharmaceutical agents and other chemicals in sewage pose a considerable concern when one considers the potential for inadvertent exposures through treated water. On the flip side, wastewater can also provide a wealth of economical and accessible epidemiologic data on common drug products consumed and excreted into community sewage systems. Now researchers have successfully tested a new "sewage epidemiology" analysis strategy to obtain near real-time information on community usage rates of drugs, allowing trends and patterns to be promptly monitored [*EHP* 116:1027–1032; Zuccato et al.].

Many drug usage studies focus on prevalence data—reported use rates based on the integration of population surveys with medical records, drug production and seizure rates, and crime statistics. But obtaining information through these channels can often be time-consuming and the accuracy questionable, as the data are based partly on self-reported use. Using a novel approach first proposed in 2001, the researchers in the current study gathered data from sewage treatment plants in Milan (Italy), Lugano (Switzerland), and London (England) to obtain information on community-wide consumption of cocaine, heroin, cannabis, and amphetamines.

The investigators collected composite samples of untreated wastewater from major sewage treatment plants in each of the

cities every 20 minutes for 24 hours in a time-proportional mode and pooled the samples using a computer-controlled device. They also tested field data from a given treatment plant for reproducibility over time: samples were taken on consecutive days for 1 week on 3 different occasions in Milan and Lugano, and on 2 days at 2 major plants in London. Wastewater samples were analyzed by liquid chromatography–tandem mass spectrometry, which measured drug residues using a highly selective multiresidue assay.

This new testing method enabled the research team to accurately measure the drugs in wastewater samples using objective quantitative data—drug concentration, wastewater flow rate, and population size—and to acquire near real-time reporting of results because of the short 1- to 2-day completion time for mass spectrometric analysis of samples. The new approach also makes it possible to integrate wastewater monitoring data with other information on drug use to obtain more refined estimates of community consumption patterns and user profiles.

The authors note this approach has certain limitations, including lack of data regarding the number of drug users in a given community, but say that the results on overall consumption rates compare reasonably well with official prevalence-based figures. For the sake of accuracy, detailed information would be needed on the metabolism and kinetics of any compound for which the approach is used. Furthermore, it can be difficult to accurately characterize "typical" users of certain pharmaceuticals or drugs. However, the authors state that with further testing, the method could be used in future research to provide real-time epidemiologic data for application to other public health issues. —Tanya Tillett

Alternative Mechanism for PFOA?

Trout Studies Shed Light on Liver Effects

Perfluorooctanoic acid (PFOA), used to make a class of industrial chemicals that are widely used in products such as textile coatings and flame retardants, is known to be a potent hepatocarcinogen in rodents. Until now the only mechanism of action for PFOA identified in rodent studies has been peroxisome proliferation, a well-characterized form of oxidative stress. Humans are reportedly insensitive to peroxisome proliferation; however, concerns remain that PFOA may cause adverse effects in people as well as in laboratory animals. Using rainbow trout as a model for chemically induced liver cancer in humans, a team of researchers suggest a new mechanism for the carcinogenicity of PFOA that does not involve peroxisome proliferation [*EHP* 116:1047–1055; Tilton et al.].

The investigators compared the hepatocarcinogenic potential of PFOA against the structurally diverse peroxisome proliferators cloribrate (CLOF) and dehydroepiandrosterone (DHEA), identifying mechanisms of carcinogenesis from hepatic gene expression

profiles phenotypically anchored to tumor outcome. Trout were fed PFOA in the diet for 30 weeks for tumor analysis. The investigators subsequently examined gene expression by cDNA array in animals fed PFOA, DHEA, CLOF, or 17 β -estradiol (E_2 ; a known tumor promoter) in the diet for 14 days.

The study showed that PFOA and DHEA treatments significantly increased liver tumor incidence and multiplicity; CLOF showed no effect. However, carcinogenesis was independent of peroxisome proliferation as measured by the lack of peroxisomal β -oxidation and catalase activity. On the contrary, both PFOA and DHEA resulted in estrogenic gene signatures closely resembling that of E_2 . CLOF, however, regulated no genes in common with E_2 .

Although the current study did not identify a threshold for the estrogenic effect of PFOA, the results indicate that PFOA is weakly estrogenic in trout and that its association with trout liver cancer may be related to disruptions in estrogenic signaling. More studies are needed to assess the potential for PFOA-mediated carcinogenesis in other species that are insensitive to peroxisome proliferation. Considering the mechanism identified in this study, the consequences of hormone-related effects by PFOA should be evaluated in other tissues, models, and sensitive life stages. —Ernie Hood



Mt. Shasta strain rainbow trout (*Oncorhynchus mykiss*)