Research Brief 178: Arsenic Just as Risky Ingested as Inhaled

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Background:

Lung cancer is the leading cause of death associated with arsenic exposures, exceeding mortality from bladder cancer, kidney cancer, and cardiovascular disease. Inhaled arsenic was linked to lung cancer in miners as early as 1879, and in 1980 the International Agency for Research on Cancer (IARC) determined there was sufficient evidence to identify inhaled inorganic arsenic as a human lung carcinogen. In 2004, the IARC listed arsenic in drinking water as a cause of lung cancer, making arsenic the first substance established to cause human cancer through two unrelated pathways of exposure.

Arsenic also increases the incidence of non-malignant pulmonary disease. Dr. Allan H. Smith at the University of California, Berkeley SRP is leading an effort to use a combination of traditional epidemiological studies and novel biomarkers of exposure, metabolism and susceptibility to investigate both short term and long term pulmonary effects of arsenic exposure. His research group has determined that people exposed to arsenic in drinking water as young children or *in utero* are particularly susceptible to both the malignant and non-malignant pulmonary effects of arsenic. (See Research Brief 137)

Inhalation is the known pathway of exposure for all other established human lung carcinogens, including cigarette smoking, asbestos, chromium, silica dust, nickel, and radon.

In a recent study, Dr. Smith's group compared lung cancer risks from inhalation and ingestion of arsenic. Because inhalation results in a more direct exposure to the lung and is the route of exposure for other known lung carcinogens, the researchers hypothesized that that inhalation risks would be much higher than those resulting from ingestion.

Advances:

Dr. Smith analyzed and compared findings from two epidemiological studies on lung cancer resulting from arsenic exposure. The first was an occupational cohort study of arsenic inhalation conducted at the Tacoma, Washington smelter. The second was a case-control study of ingestion of arsenic conducted in northern Chile where, because of the unusual municipal water system, researchers could determine the drinking water arsenic concentration for each person in the study.

Dr. Smith plotted dose-response relationships using lung cancer relative risk estimates as the measure of effect, and urinary arsenic concentrations during exposure as the biological marker of the absorbed dose rate for both inhalation and ingestion of arsenic. He compared the slopes of the linear regressions to determine whether exposure via inhalation or ingestion resulted in the greater lung cancer risk. It is important to note that although cumulative dose is often used as a measure of exposure in cancer studies, this study used urinary arsenic concentration, which gives a measure of the *dose rate*. Dr. Smith believes when relative risk is the measure of effect, then in steady state (i.e. with long-term exposure and after appropriate latency) relative risk will be determined by dose rate, rather than by cumulative dose. Both study populations had received long-term steady-state exposures to arsenic.

Dr. Smith was awarded the John Goldsmith Award by the International Society of Environmental Epidemiology at their August 2009 Annual Conference in Dublin, Ireland. The Goldsmith Award is presented for outstanding contributions to the knowledge and practice of environmental epidemiology.

While it seems logical to expect that the risks from inhalation with direct exposure to lung cells would be much higher than the risks from ingestion, Dr. Smith found that lung cancer risks are ***not dependent upon the exposure pathway***, but rather on the absorbed dose.

Dr. Smith suggests the explanation could be related to arsenic metabolism. The primary route of metabolism of internally absorbed inorganic arsenic is methylation. Recent evidence suggests that the first step of methylation may be one of activation rather than detoxification. Dr. Smith concludes that one potential reason for the absorbed dose of arsenic determining the lung cancer risk is that the inhaled arsenic may first need to methylated, and that this step may not occur in the lung cells themselves. In other words, inhaled arsenic may need to enter the circulation, get methylated in some other part of the body, and then return to the lung, where it may then exert a carcinogenic effect. But a simpler

explanation, he suggests, is that what determines risk with steady state exposure is the steady state concentration of arsenic *inside* lung cells, and this in turn would be related to the dose of arsenic absorbed into the body, not the pathway of exposure.

Significance:

This finding is pertinent to the consideration of biological mechanisms for arsenic-induced lung cancer, and also to the assessment of population risks, which appear to be independent of the pathway of exposure.

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To learn more about this research, please refer to the following sources:

Smith, Allan H., A. Ercumen, Y. Yuan, and C.M. Steinhaus. 2009. Increased lung cancer risks are similar whether arsenic is ingested or inhaled. *Journal of Exposure Science and Environmental Epidemiology*. 19(4):343-348. doi:10.1038/jes.2008.73

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