The following request for clarifications were submitted to Dr. Joseph Graziano and Dr. Joshua Hamilton in response to some of the updated public health information presented in Boston.

We thank Drs. Graziano and Hamilton for their responses.

Inorganic As does not cause tumors. [question about basis for this statement]

Clarification: Inorganic arsenic (iAs) is clearly a human carcinogen and is almost certainly an animal carcinogen. But technically iAs as a single agent has so far been negative for tumorigenicity in adult animals following the standard NTP bioassay protocol or similar experimental designs. However, it has been shown to cause tumors in offspring of mothers exposed to iAs, i.e., it is a transplacental carcinogen (see recent study of Michael Waalkes et al. NIEHS-NTP). It should be noted that, in general, transplacental carcinogens require a much lower dose and a much shorter time to cause tumors in offspring exposed via the mother than the same agent given to adults -- "a tenth of the dose in a tenth of the time" is an old rule of thumb for organic carcinogens that are also transplacental carcinogens. Therefore the negative results for iAs in adult animals may be a dose- and time-related issue rather than true negativity. iAs has been shown in animals to increase tumors in a potentiating manner when combined with other known carcinogenic agents (e.g., iAs plus UV irradiation, see recent studies of Toby Rossman et al., NYU SBRP) similar to the synergies seen in humans (e.g., iAs plus sunlight, iAs plus cigarette smoking, iAs plus other occupational lung carcinogens).

It is also well established as a known carcinogen in humans, although whether or not as a single agent, at least at low doses, remains an open question - for example, Margaret Karagas et al. (Dartmouth SBRP) have shown in recent studies that there is increased risk of skin and bladder cancer in the New Hampshire population, but the excess risk is only seen in smokers.

Trimethyl trivalent As is most toxic form. [exposure route question]

Clarification: Exposure to the trimethyl trivalent form of As occurs only from the in vivo methylation of iAs. The biomethylation of iAs generates mono-and dimethyl arsenic, MMA and DMA, respectively, which are more readily excreted than iAs. Indivuduals whose urine contains relatively higher proportions of DMA and lower proportions of MMA have been reported to be at decreased risk for skin lesions, skin cancer and bladder cancer.

Thus, methylation of iAs has traditionally been considered to be a detoxification pathway. However, a growing number of experimental studies indicates that the trivalent forms of MMA and DMA may be more potent than their pentavalent forms, or iAs. (See Gamble et al, EHP 13:1683, 2005 for a review).

Arsenate goes more to bone; arsenite goes more to skin, nails, hair [question about exposure route for this observation]

Clarification: The tissue distribution of radiolabeled i.v. arsenite and arsenate has been carefully studied by autoradiography in mice and hamsters by Lindren et al (Acta Pharmacol et Toxicol 51: 253-265, 1982. For example, the authors studied mice at 0.5, 6, 24 and 72 hours after i.v. arsenite injection.

While liver, gall bladder, duodenum and kidney had the highest amounts of radioactivity at 0.5 hours, the organ that contained the most radioactivity at 72 hours was skin. After i.v. administration of arsenate, the skeleton contained the highest amount of radioactivity at 72 hours.

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