Re: Arsenic Carcinogenicity Testing

In their letter to EHP, Huff et al. (1) maintained that arsenic is still viewed as "a paradoxical carcinogen; that is, carcinogenic to humans but not to laboratory animals," and that this paradox will be believed until carcinogenicity of arsenic is demonstrated in animal experiments such as "long-term inhalation studies using arsenic trioxide."

Huff et al. (1) seem not to take into consideration, however, that a researcher never has at his disposal an animal population commensurable with human populations for which even low carcinogenic risk may be attributed to an exposure, based on epidemiologic data, with a sufficient statistical significance. Even under carcinogenic exposure, even most common cancers are still rather rare events. For example, an additional 50 lung cancers per 100,000 workers exposed to arsenic trioxide aerosol in copper smelters would constitute a very high risk level, while probably no cancer would be detected after exposing 100 rats to the same aerosol, provided the risk is the same. To attempt to circumvent this statistical obstacle, we might expose rats to much higher concentrations of As2O3, but under such an exposure, development of a severe intoxication would be highly probable, and rats with a dramatically shortened life span might never survive until the appearance of cancer. The same argument is valid if drinking water is used as the medium for administering arsenic.

It seems much wiser to use experimental models, giving opportunity to concentrate a sufficiently high and long-term exposure on a small part of a target organ only, thus reducing systemic toxicity of the tested chemical to a minimum. Of course, such a model would be difficult to use directly for any standard setting, but it would be adequate for proving that the chemical is carcinogenic (at least for one organ).

Twelve years ago we published results of such an experiment (2), which Huff et al. (1) failed to mention in their brief overview. The English version of the summary of our paper (verbatim as translated by the publishers) is as follows:

Out of 18 albino rats which survived 17–24 months after implantation in a partially isolated glandular stomach compartment of a perforated polyethylene capsule containing 8 mg arsenic trioxide in a fat wax mixture as vehicle, two developed muconodular adenocarcinoma and one - mucoid cystic adenocarcinoma in that gastric compartment; metastasis in the liver was detected in one animal. No malignant tumors were found in 9 rats with the same post-surgical survival time after implantation of a control capsule containing the same mixture without arsenic. Since spontaneous gastric cancers virtually fail to appear in laboratory rats, nor have they ever been reported by other authors after control capsule implantation but developed in some rats after implantation of a carcinogen-containing one, the results of the present investigation may be interpreted as an experimental proof of the carcinogenicity of arsenic which was previously assumed on epidemiologic evidence.

Bullock and Curtis (3) reported one gastric cancer per 33,000 rats. Anisimov et al. (4) found 63 spontaneous malignant tumors but no gastric cancer in 443 rats (average age 723 ± 16 days for 213 males and 735 ± 14 days for 230 females) bred at the same farm from which our rats were obtained.

We also obtained one gastric cancer from rats implanted with calcium arsenate and one from those implanted with natural arsponyrite (5). The latter is of a special interest, as it was demonstrated in an epidemiologic study that the higher the arsenic content (mainly as the arsponyrite) in the ore deposits and in mine dusts, the higher the cancer mortality in gold-miners (5).

It is a pity that language and other barriers made our papers unknown to Western colleagues, but it is never too late to learn.

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Arsenic: Evidence of Carcinogenicity in Animals

We are grateful to Katsnelson for reminding us about his paper on arsenic implantation and local gastric cancer published some 12 years ago (2). We were indeed aware of their published work, which was contained and summarized in an IARC Monograph carcinoenicity evaluation of arsenic (2), and cited in our review (3).

However, while the collective evidence of carcinogenicity on arsenic appears quite close to being considered sufficient evidence in experimental animals (2–4), an adequate and definitive long-term (30+ months) experiment on arsenic (and specifically arsenic trioxide) has not yet been done, especially not by inhalation. We believe this should be accomplished to settle the debate whether arsenic is the only human carcinogen that has not been shown to likewise convincingly cause cancer in laboratory animals. Further, the argument that inorganic arsenic is a multiorgan carcinogen in humans that will not be carcinogenic in animals because of differences between humans and rodents in methylation detoxification capabilities has yet to be proven. Arsenic is clastogenic in both humans and animals, and mechanistically, arsenic appears to be a late stage carcinogen (5,6).

Regarding alleged "paradoxical" carcinogens, in the 1970s and 1980s arsenic and benzene, long considered carcinogenic in humans, were touted as being exceptions to the animal–human paradigm and were thus used to discredit bioassays because of posed nonconcordance with respect to a lack of carcinogenicity in animals. Perhaps similar to arsenic, nearly 16 bioassays had been done on benzene with little or no evidence of carcinogenicity in animals. Yet, until Maltoni and colleagues (10,11) and Huff et al. (12) showed unequivocally that benzene is a potent multispecies, multistrain, multisite carcinogen, many indicated that long-term bioassay results were not relevant to human cancer risks. Thus, should arsenic be considered as the only known human carcinogen with less than sufficient correlative evidence of carcinogenicity in animals? The scientifically appropriate answer is "no," not because arsenic is not carcinogenic to animals, but simply because definitive studies have not yet been done to unequivocally answer the question. Conversely, we know that for nearly 30 agents the evidence of carcinogenicity was first observed in animals (and unheeded) and only subsequently detected in humans (13,14), in fact, all known human carcinogens that have been tested adequately are also carcinogenic to animals (15–17).

Experimental carcinogenicity studies on arsenic, so far, have been either inadequately done (short duration, incomplete reporting, limited pathology), poorly designed (inappropriate or no controls), or any marginally positive results have been confounded by other experimental factors (2,3,18). Few relevant studies have been reported since the last International Agency for Research on Cancer (IARC) evaluation of arsenic in 1987 (19–22), and these were primarily concerned with arsenic as a tumor promoter or in combination with other agents. None of these studies are considered adequate for determining whether arsenic, as a single agent, is carcinogenic to animals (3,23).