Factors Affecting the Impact of Exposures to Metals

Understanding the toxicological impacts of exposures to environmental contaminants is a critical public health challenge. This challenge is intensified by the fact that we may be exposed, either concurrently or sequentially, to a large number of toxic agents throughout our lifetime. Researchers at the New York University School of Medicine Superfund Basic Research Program have identified yet another factor to be considered in studies to define the health effects of environmental exposures to metals – interactions with ultraviolet radiation exposure that enhance carcinogenesis.

Epidemiological studies have shown that inorganic arsenic (arsenite and arsenate) in drinking water increases skin, lung, bladder, and possibly other cancers in humans. However, inorganic arsenic alone does not cause skin cancer in animals. Dr. Toby Rossman hypothesized that arsenite is a co-carcinogen requiring a carcinogenic partner. To test this hypothesis, she exposed groups of hairless mice to arsenite alone; UV alone; or arsenite + UV. The hairless mouse model allows researchers to easily monitor the appearance of cancers over time. Dr. Rossman found that untreated mice and mice treated with arsenite alone did not develop tumors. Mice treated with UV alone or with arsenite + UV developed locally invasive squamous cell carcinomas. Mice exposed to arsenite + UV had a ***dose-related increase in skin cancers*** compared with mice exposed to UV alone. The tumors in mice treated with arsenite + UV appeared earlier and were larger and more invasive than those in mice given UV alone. This is the first demonstration of a linear relationship between arsenite concentration and enhancement of squamous cell carcinomas in UV exposed mice and is particularly interesting as the enhancement occurred at arsenite doses well within the range of human exposures.

Selenium is reported to counteract some of the effects of arsenic *in vivo* and *in vitro*. Dr. Rossman investigated the hypothesis that selenium deficiency may exacerbate arsenic toxicity and carcinogenicity, which has been suggested by cancer rates in some parts of the world with high arsenic in the drinking water and low selenium levels in soil. Dr. Rossman used the hairless mouse model and found that treatment with organoselenium compounds prevented the arsenite enhancement of UV-induced skin cancer, but had a negligible effect on UV alone-induced skin cancer. *In vitro* experiments showed that organoselenium compounds blocked the delayed mutagenesis induced by arsenite, as well as spontaneous mutagenesis. Dr. Rossman believes that the antimutagenic and anticarcinogenic effects of selenium against arsenite may occur via the antioxidant action of selenoproteins.

In studies of similar design, Dr. Max Costa investigated the impact of exposure to hexavalent chromium [Cr(VI)] in drinking water on susceptibility to UV-induced skin cancers. Occupational exposure to chromate compounds via inhalation has been demonstrated to cause an increase in respiratory cancers, but the carcinogenic hazard of *drinking water* exposure has not been established. Dr. Costa exposed groups of hairless mice to Cr(VI) alone; UV alone; or Cr(VI) + UV and found that no skin tumors occurred untreated mice or mice treated with Cr(VI) alone. There was a ***dose-dependent increase in the number of skin tumors*** in mice treated with Cr(VI) + UV compared with mice exposed to UV alone. The levels of Cr(VI) that produced this effect were at the environmentally relevant level of 1-5 ppm. Dr. Costa suggests that exposure to UV radiation increases the amount of chromium that reaches skin cells – and if more chromium gets into the cells, the potential for oxidative stress damage is increased. This is the first study that shows that Cr(VI) can induce cancer by drinking water exposure.

Because we are rarely exposed to only one carcinogen at a time and are frequently exposed to UV radiation, these findings have important implications with regards to the potential carcinogenic hazards of low levels of chromate and inorganic arsenic in drinking water.

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To learn more about this research, please refer to:

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