

Cancer risks for humans from exposure to the semiconductor metals

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FOWLER BA, YAMAUCHI H, CONNER EA, AKKERMAN M. Cancer risks for humans from exposure to the semiconductor metals. *Scand J Work Environ Health* 1993;19 suppl 1:101—3. Of the semiconductor metals, only arsenic has been extensively studied as a human carcinogen and systemic toxicant. Recent studies have shown, however, that gallium, arsenic, and indium are capable of producing marked alterations in cellular gene products. After acute in vivo administration indium and thallium have been shown to produce decreases in the activity of some drug-metabolizing enzymes dependent on cytochrome P-450; therefore these metals would be capable of interfering with the metabolism of organic carcinogens. Selenium is essential for the activity of the enzyme glutathione peroxidase, which modulates the active intermediates generated by drug-metabolizing enzyme systems. Germanium produces toxicity in a number of organ systems. Antimony produces lung and circulatory system effects. Overall, available data suggest that these metals or metalloids are capable of biologically altering several cellular defense mechanisms involved in the carcinogenic process and that further studies are needed to determine the associated risks.

Key terms: antimony, arsenic, gallium, germanium, indium, selenium, thallium.

Currently, there is a relatively small toxicology data base for elements such as gallium, indium, thallium, germanium, arsenic, antimony, and selenium, which are used to produce semiconductors. The following review is intended to provide an overview of available studies on these elements from the perspective of carcinogenic potential. Particular attention has been focused on alteration in cellular defense mechanisms for handling organic carcinogens and alterations in cellular gene expression. The effects of these elements on such cellular processes currently appear to be among the most relevant with regard to low-dose exposure situations.

The element arsenic and its various chemical forms and oxidation states have been the most extensively studied of the semiconductor materials, and numerous international groups have evaluated its carcinogenic potential (1, 2). The overall results of these evaluations have concluded that exposure to inorganic arsenic particles as trivalent arsenic in air is associated with an increased incidence of lung cancer, while exposure to organic arsenic species in drinking water is associated with an elevated incidence of skin cancer in exposed human populations. Experimental studies concerning arsenic carcinogenesis in animals have been positive in the presence of trivalent arsenic, and more positive for trivalent

arsenic plus other carcinogenic agents such as benzo[a]pyrene (3, 4).

Studies from several laboratories (5—7) have shown that exposure to trivalent arsenic causes the induction of several stress proteins both in vitro (5, 6) and in vivo (7). Among the identified gene products (8) is the 32-kDa stress protein known as heme oxygenase. These data indicate that trivalent arsenic produces marked alterations in gene expression patterns in several cell types, and therefore may create a situation that permits other carcinogenic substances to act more effectively at the cellular level.

Indium

Indium is a major component of numerous electronic devices, including high-speed III—V semiconductors such as indium arsenide. Previous studies (9—11) have shown that indium causes the induction of heme oxygenase, which is associated with the reduction of enzyme activities dependent on cytochrome P-450. This metal has also been shown to be a potent inhibitor of aminolevulinic acid dehydratase in several tissues (9), and subcutaneous injection of indium arsenide particles has been found to inhibit this enzyme markedly in blood and produce an increased excretion of aminolevulinic acid in the urine of hamsters. Indium exposure is also associated with a general suppression of protein synthesis (7) that indicates that several effects occur after exposure to this agent. These data suggest that the carcinogenic properties of indium are probably linked to alterations in the synthesis and maintenance of enzyme systems which metabolize organic carcinogens. A compromise in the

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ability of these metabolic systems would lead to altered cellular responses to organic carcinogenic substances.

Gallium

Gallium is another element which is used in the production of high-speed semiconductors such as gallium arsenide and as an antitumor agent. This element is a potent inhibitor of protein synthesis and the heme pathway enzyme aminolevulinic acid dehydratase (12, 13). More recent studies (6) have shown that gallium causes several alterations in gene expression in renal proximal tubule cells in vitro, including the induction of heme oxygenase, which, as has already been noted, is the 32-kDa stress protein (8). Taken together, these data indicate that gallium, like arsenic, is capable of producing alterations in both the heme biosynthetic pathway and the cellular gene expression, which are linked in at least one place by the induction of heme oxygenase. This information has led us to the hypothesis that, in fact, the responses of these two cellular defense systems are related to each other at a very basic biochemical level.

Thallium

Thallium is another metal which is known to produce alterations in cellular gene expression machinery and the heme biosynthetic pathway (14, 15). In this case ionic thallium appears to interfere with the process of ribosomal assembly. This interference results in a number of structural changes in the endoplasmic reticulum in liver cells after acute in vivo injection, which is associated with alterations in the activities of several heme-pathway and heme-dependent enzyme systems (14). As with the other metals or metalloids under discussion, it appears that this element is capable of interfering with a number of subcellular systems and that the consequences of these effects may predispose target cell populations to eventual carcinogenic susceptibility.

Germanium

Studies using germanium-based antitumor agents have shown that this element is capable of inhibiting deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis in in vitro systems with resultant impairment of cellular replication and cell killing (16). Germanium compounds are also known to be immunosuppressive to both the humoral and cellular aspects of immune function (16). There are also indications that germanium-based agents prolong opiod analgesia and therefore that this element, like the others already discussed, may interfere with drug-metabolizing systems (16). All of the aforementioned general mechanisms have implications for potentially fostering the carcinogenic response, but

further research is needed to determine whether such effects have any consequences in human populations potentially exposed to germanium materials, for example, workers in the electronics industry.

Antimony

Antimony compounds are known to produce toxicity to several organ systems, including the liver, lung, and kidney. The mechanisms of toxicity are not as well characterized as those known for other metalloids, such as arsenic (17). Antimony compounds have been shown to exhibit positive results in in vitro mutagenicity test systems (18). There is one report (19) of the carcinogenicity of antimony trioxide. Results of these studies generally indicate that antimony has the potential to produce cellular alterations that could potentially lead to a carcinogenic response, but definitive studies are currently not available.

Selenium

In the case of selenium, there is evidence (20) that selenium administration exerts a generally suppressive effect on a variety of chemically induced tumors in rodent model systems.

One possible mechanism involves the role of this element in the activity of glutathione peroxidase, which is known to participate in the metabolism of oxygen radicals such as those generated by several organic carcinogens. The toxicity of selenium to animals appears to occur at higher concentrations in the diet and appears to involve several organ systems (21). The biochemical mechanisms of this toxicity have not been very well studied.

Summary

The preceding discussion is a brief overview of the toxicity of several metals or metalloids whose use may be expanding due to their increased presence in the manufacture of semiconductors, superconductors, and other electronic devices. In contrast with metals such as lead, cadmium, and mercury, relatively little is known about the mechanisms of toxicity of most of these agents, either alone or more commonly as binary or ternary compounds. Therefore a great deal of future research is needed before one can accurately predict the consequences of human exposure to compounds of these metals or metalloids in either the work or general environment if devices containing these materials are not recycled. A major component of these studies will be the inclusion of chemical-specific biomarkers of both exposure and effect for these elements alone or in mixtures.

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