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Review

Possible Health Hazards Associated with the Use of Toxic Metals in Semiconductor Industries

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Abstract: Possible Health Hazards Associated with the Use of Toxic Metals in Semiconductor Industries: Swaran J.S. FLORA. Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Gwalior, India—Gallium Arsenide (GaAs), Indium Arsenide (InAs) and Indium Phosphide (InP) are the intermetallic compounds that are recognised as a potential health risk to workers occupationally exposed to their dust. Exposure to these semiconductor compounds in the microelectronic industry can occur during the preparation of material, cleaning and maintenance operations for quartz glassware and during cleaning of the reactor. The toxic effect of the intermetallic semiconductors appears to occur due to inhalation or oral exposure and may result in poisoning. Assessment of risk to workers engaged in GaAs/InAs production is difficult due to the lack of data on the toxicity of these compounds. Their toxicity is mainly estimated on the basis of inorganic arsenic because it is now well known that GaAs and InAs dissociate into their constitute moieties and exert adverse effects on the haematopoietic and immune systems. As their toxicity is still not very well understood the treatment also remains to be elucidated.
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Key words: Gallium arsenide, Indium arsenide, Indium phosphide, Metal distribution, Biochemical changes, Experimental evidence, Chelation treatment

In the defence microelectronic industry, silicon was previously the substrate predominantly used, but in recent times a number of other semiconductor materials (particularly III–V intermetallic semiconductors) have been introduced which have an increasing number of applications. Gallium arsenide (GaAs) is one of the substrates which have superior properties for making high frequency devices, and photon emitters followed by gallium phosphide (GaP), indium phosphide (InP) and indium arsenide (InAs). These III–V intermetallic semiconductors are crystalline and intermetallic compounds. They are prepared by condensing vapours of the elemental forms of the metalloids. They have found distinct and continually expanding application in the semiconductor industry. Such a demand can be expected to result in an increase in the production and processing of ingots and wafers, which has the potential to expose much of the semiconductors industry to these toxic metals. The chemical from of the intermetallic does not appear to be as important for toxicology as the chemical forms of its dissolution products. In the manufacture of these semiconductors there are four major steps:crystal growth, wafer processing, epitaxy production and device fabrication. In future these compounds are going to be extensively used in the development of supercomputers, telecommunication systems, light emitting diodes and semiconductor lasers[1, 2]. GaAs has a distinct advantage in electronic speed compared with silicon and is therefore increasingly used for satellite communication systems and supercomputers. Several favourable properties as compared with silicon based devices suggest that GaAs and such other intermetallic substrates may find applications in military, space, telecommunication and supercomputing systems. All these extensive uses of GaAs will inevitably lead to an increase in the exposure of workers manufacturing these products.

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Possible Routes of Exposure

Exposure to these intermetallic substrates (semiconductors) may occur during cleaning and maintenance operations for quartz glassware and during cleaning of the reactors. Exposure may also be expected during cropping, slicing, lapping, polishing, and backlapping and wafer-saving steps. Disposal of the waste products and recycling of these materials have also not yet been discussed. Exposure to airborne particulate of GaAs may therefore be potential health hazards in the

semiconductor industry. The toxic effects of the intermetallic semiconductor materials appear to occur primarily after inhalation exposure, although oral exposure to high doses may also result in toxicity. Assessment of the risk to these workers from GaAs exposure is further complicated due to the lack of toxicity data available for this compound and, as mentioned above, is mainly regulated on the basis of inorganic arsenic toxicity. It is now well known that both GaAs and InAs dissociate into its constitutive moieties both *in vitro* and *in vivo*[3–6] and arsenic is a well-known toxic metal, so that one should not take the toxicity of these intermetallic semiconductors lightly.

Bioavailability, metabolism and excretions of most of the III–V intermetallic compounds are not well known. Bioavailability may depend on their dissolution rates and chemical properties. The reported acute lethality of these III–V intermetallic compounds is of low order. The oral LD_{50} of GaAs in mice and rats is more than 15 g/kg, whereas the threshold for acute effects is around 7 g/kg[7]. The threshold for acute effects (lowest published lethal dose) of inhalation of GaAs aerosol for 4 hours has been reported to be 152.5 mg/m^3. For Indium antimonide the reported LD_{50} is 3.7 g/kg by the intraperitoneal route whereas that for indium arsenide it is around 15 g/kg. For GaP the reported LD_{50} is 8 g/kg[7]. The oral LD_{50} of metallic indium was 4200 mg/kg for rats and that of intraperitoneal and oral LD_{50} of InP was reported to be more than 5000 mg/kg.

Effects on Biological Systems

The absorption of GaAs and InAs appears to be accompanied by the formation of arsenic oxide. Numerous reports have indicated that pulmonary exposure to GaAs and InAs dust represents a potential health hazard, but the degree of risk has not yet been fully defined. Recent experiments have investigated the acute toxicity of GaAs and InAs particulate fractions which are soluble under physiologically relevant *in vitro* conditions and produce a dose related increase in blood arsenic levels. When delivered to rats by either the oral or intratracheal route, exposure resulted in decreased body weight as well as both quantitative and qualitative changes in urinary porphyrin excretion[7–9]. In addition to the above, there have been a number of other studies demonstrating the solubility of GaAs particles *in vivo* and the tissue distribution and excretion patterns of Ga and As over time after the administration of GaAs particles via a variety of routes[10]. These results lead to the conclusion that particles of GaAs and InAs are degraded *in vivo* to release their constitutive elements, which are then distributed to major target organs. But Zheng *et al.*[11] indicated poor absorption of indium following repeated oral or intratracheal instillation of indium phosphide, suggesting that indium is unlikely to accumulate in the body after InP exposure. Fecal excretion is a major route for its elimination. Based on the literature available it is now well known that GaAs produces a definite adverse effect on at least three major body systems, i) pulmonary, ii) haematopoietic and iii) immune.

Pulmonary Effects

Toxicity of inhaled gallium arsenide compounds has been reported in a number of reports in the recent past[12–15]. It has been suggested that particulate fractions with a mean count and volume diameter of 8.3 and 12.67 μm were soluble under physiologically relevant *in vitro* conditions[12]. The intratracheal administration of this GaAs particulate fraction was relatively more toxic than equivalent doses given through the oral route and results in increased lung weight[12]. Webb *et al.*[12] also evaluated the toxicity of Ga_2O_3, As_2O_3 and GaAs after the intratracheal instillation of these particles in rats. They found that the toxicity ranking was GaAs>As_2O_3>Ga_2O_3 and suggested that the pathological responses observed in lungs were likely to be primarily due to arsenic. The lesions in lungs due to Ga_2O_3 were not remarkable. Ohyama *et al.*[13] observed severe lung lesions, and survival was also shortened significantly in animals intratracheally exposed to GaAs particle (0.25 mg × 15 times/animals) compared to controls. Goering *et al.*[5] also reported histopathological changes characterised by multifocal granulomas and type II pneumocyte hyperplasia after single intratracheal instillation of GaAs (50, 100 or 200 mg/kg). Indium arsenide (InAs) and indium phosphide (InP) were also reported to produce histopathological changes in lungs of hamsters[14, 15]. The major changes include alveolar and bronchiolar cell hyperplasia, pneumonia, and emphysema and metaplastic ossification after InAs exposure in rats and hamsters. Kabe *et al.*[14] using mice and oral and intraperitoneal (i.p.) routes of exposure reported a dose dependent increase in lung weight. Extramedullary granulopoiesis, eosinophillic exudates and mononuclear cells were seen in the pulmonary alveoli after i.p. administration. But the p.o. administered mice showed no clear relationship between the dose and biological effects. On the other hand, InP is reported to cause pulmonary inflammation and the particles remained in the lower airways for nearly seven days[16, 17]. A dose dependent increase in superoxide dismutase (SOD) and the lactate dehydrogenase (LDH) activity in the bronchioalveolar lavage fluid (BALF) was also found in InP exposed rats[17], but these studies clearly indicate adverse effects of these semiconductor materials on the pulmonary system in experimental studies. Well planned detailed studies on subjects handling these materials in the industry are still lacking.

Haematopoietic Effects

Chemically induced disturbances of the heme biosynthetic pathway have been utilized for many years as a class of biomarkers for detecting the sublethal toxicity metals, but very few reports have indicated perturbation of heme metabolism by binary metal compounds in groups III and V. There have been a number of animal studies reported recently on the effects of GaAs on porphyrin metabolism. Goering *et al.*[5] first reported that GaAs after a single intratracheal instillation produced a dose dependent inhibition of blood delta - aminolevulinic acid dehydratase, (ALAD), an important enzyme in the heme biosynthetic pathway. They reported that the activity decreases to 5% of the control at a dose of 200 mg/kg on day 6 after a single exposure. Urinary aminolevulinic acid (ALA) excretion was also maximum 3 to 6 days post exposure and recovered to the control value by day 18. These authors further suggested that gallium is the primary inhibitor of ALAD after dissolution of GaAs *in vivo* and that competition for or displacement of zinc as the enzyme active site may be involved in the mechanism of inhibition. These data were later supported by a brief report by Flora and Das Gupta[3]. They reported a dose dependent inhibition of blood ALAD, whereas a moderate increase in blood zinc protoporphyrin (ZPP) and urinary ALA excretion as observed after a single oral exposure on days 1, 7 and 15. A dose dependent increase in the blood arsenic concentration was also noticed, but gallium content was not detectable in animals exposed to a low oral dose of GaAs. Conner *et al.*[8] recently observed that InAs and constitutive elements results in a unique urinary porphyrin excretion profile. They reported an inhibition of erythrocyte ALAD but no change in hepatic ALAD activity. In contrast renal ALAD was found to be statistically decreased by As at first but increased at a later stage after a single exposure. Studies of urinary porphyrin excretion patterns in animals treated with InAs showed marked and early 2–4 fold increases in the excretion of penta, hexa and heptacarboxyl porphyrin at 1–5 d, indicating that both In and As are biologically active after InAs exposure and that enzymes in the heme pathway such as ALAD may be very useful as markers of exposure. Nevertheless, we still strongly believe that a few more detailed studies are needed, particularly on different animal models and with various doses, but it is desirable to suggest that measurement of the activity of blood ALAD and urinary ALA excretion could be the useful early indicators of GaAs and InAs exposure. Flora *et al.*[18, 19] recently conducted a more detailed study with the rat as the experimental model and found that GaAs had a strong effect on heme synthesis but only a mild secondary effect on major physiological variables (viz., blood pressure, respiration, heart rate and neuromuscular transmission) was noticed. Furthermore, the peak adverse effects were reached at day 7 after exposure compared to observations at two other times i.e., day 1 and 15. Previously, Webb *et al.*[9] also indicated that the urinary porphyrin concentration was changed over the 14 d study and accompanied by a decrease in body weight. They further concluded that the urinary uroporphyrin concentration was greater than the coproporphyrin concentration and may therefore serve as a sensitive indicator of GaAs exposure. It is therefore evident from the abovementioned studies that these semiconductor intermetallic substrates affect the heme synthesis pathway and they may also serve as an early indicator of toxicity. But in order to be able to suggest a more specific and sensitive indicator, further detailed studies are definitely required in this area.

Immunological Effects

A number of recent reports on laboratory animals have demonstrated that the immune system is also one of the sensitive target sites after GaAs exposure. Both humoral and cell mediated sites of immunity are specifically affected[20] and all cell types involved in the generation of a T cell dependent antibody response are functionally compromised[21, 22].

The immunotoxic action of GaAs was found to occur within the first 36 h of an immune response and was shown to be a result of the toxic action of the arsenic component of GaAs[19, 23]. In addition, GaAs targets several T cell mediated immunological functions including, but not limited to, the DHR, the CTL response, the MLR and the T cell dependent humoral immune response[20, 22]. A few other recent studies have revealed that after GaAs exposure T cell proliferation was selectively targeted and that this was likely due to effects on the IL-2 receptor; the receptor for the major T Cell growth factor[24].

The exact biochemical or molecular mechanism by which GaAs produces immunosuppression is not known, although several possibilities have been proposed[21, 24]. It is now generally believed that arsenic dissociation from GaAs may be responsible for some of the immunotoxic effects and may constitute a potential risk to workers exposed to this compound[24].

The above studies therefore confirm that the immune system is a sensitive target organ for toxicity from GaAs and that such suppressive effects may play a role in the observed rate of semiconductor worker absenteeism due to illness[25]. Data regarding the effect of InAs on the immune system are lacking.

Reproductive Effects

A few recent studies by Omura and his group found that the repetitive intratracheal instillation of GaAs decreased the sperm count and increased the proportion of abnormal sperm in the epididymis of rats[26], though the effects of GaAs on spermatogenesis in the testis were

not clearly demonstrated. This group recently published a more comprehensive report in which the testicular toxicity of GaAs and InAs was examined in rats by repeated intratracheal instillation of these substances in suspension twice a week, 16 times altogether[27]. They reported a significant decrease in sperm counts and significant increase in the proportion of morphologically abnormal sperm in the epididymis of the GaAs exposed group. It was indicated that GaAs disturbed the spermatid head transformation at the late spermiogenic phases and caused spermiation failure[27]. InAs caused a sperm count decrease in the epididymis, though its testicular toxicity was relatively weak compared to with that of GaAs. Arsenic trioxide, a probable dissolution product of GaAs and InAs *in vivo* did not show any sign of testicular toxicity in this study. It could therefore be suggested that arsenic, gallium and indium play a role in the testicular toxicity of GaAs and InAs[27]. In another recently reported interesting study, these authors confirmed that among these metals, gallium might play a main role in the testicular toxicity of GaAs in hamsters[28]. They reported that the serum arsenic concentration in GaAs treated hamsters was less than half of that in arsenic trioxide treated hamsters in which no testicular toxicity was observed. It is recommended that further studies be conducted in order to examine the *in vivo* distribution of arsenic, gallium and indium in the testis to evaluate the degree of contribution of these elements to the testicular toxicity of GaAs and InAs.

Renal Effects

Goering *et al.*[5] for the first time reported that intratracheal exposure to GaAs particles could lead to both ultrastructural and biochemical manifestation of renal tubular injury. Flora *et al.*[19] reported an increase in urinary protein excretion and renal alkaine phospharase activity but the change were dose dependent. A few subsequent studies also showed marked alterations in renal tubule gene expression after *in vivo* administration of GaAs[29]. Conner *et al.*[29] and Conner[30] showed marked alterations in renal tubule gene expression after GaAs and InAs exposure. Indium administration was also reported to decrease overall protein synthesis, which is consistent with the renal accumulation of In[7].

Hepatic Effects

Webb *et al.*[10] reported impaired liver function due to arsenic dissociated from GaAs as indicated by increased urinary excretion of uroporphyrin. Flora[31] also recently reported changes in some key biochemical variables in the liver of rats exposed to various doses of GaAs, but the changes were only mild. The liver has been reported to be a target for indium[32] and arsenate[33], but there has been no information so far in the literature about the effect of InAs on the liver.

Central Nervous System Effects

There have been no detailed studies conducted so far on the effects of GaAs on the central nervous system (CNS), but Flora *et al.*[34] demonstrated changes in the steady state levels of some brain neurotransmitters. The results indicated only a moderate effect of GaAs, after repeated low level exposure, on the level of brain biogenic amines (dopamine, norepinephrine and 5-hydroxytryptamine) but a significant effect on brain and blood acetylcholinesterase (AChE) activity. Histopathological observations also revealed some mild effects, particularly in the cerebral cortex region.

Other Effects

There are no reports of effects of these semiconductor materials on other organ systems, but it is now clear beyond any doubt that GaAs and InAs particles dissolve and release arsenic. It is likely that chronic low level exposure may ultimately lead these agents to produce clinical manifestation in worker populations.

Flora *et al.*[18] reported few changes, particularly at a higher dose level, in the physiological variables, viz. blood pressure, heart rate, respiration and twitch response. The peak adverse effects were noticed at day 7 after a single exposure compared to observation at two other times (i.e., day 1 and day 15).

Biological Monitoring

There is so far no well-conducted report available in the literature about the biological monitoring of subjects handling these compounds. Yamamuchi *et al.*[35] reported a method for biological monitoring of inorganic arsenic exposure, and the chemical species of arsenic were measured in the urine and the hair of GaAs plant workers and copper smelter workers. It was revealed that the total arsenic concentration in the hair of all groups of GaAs plant workers tended to be higher than in the control groups. It is suggested that urinary arsenic levels be generally used as a biologic monitor for arsenic exposure. It is recommended that due to a possible high arsenic concentration in sea-food, the workers should be asked to refrain from eating sea food 3–4 days before being tested for arsenic in a GaAs or InAs plant. Tests for an inorganic form of arsenic in blood, urine and hair along with determination of blood ALAD and urinary ALA excretion may be conducted as a routine measure to determine arsenic exposure in such industries.

No definite data are available and no specific exposure limits have been formulated for any of the III–V intermetallic compounds. The National Institute of Occupational Safety and Health (NIOSH) issued an alert and recommended that exposure to GaAs be controlled by observing the NIOSH Recommended Exposure Limit for inorganic arsenic (2 μg/m^3 of air as a 15 min ceiling). NIOSH also recommended that the concentration of GaAs in air be estimated by the determination of arsenic[12].

Treatment

As the toxicology of GaAs is still not very well understood or clearly defined, the treatment also remains doubtful. British Anti Lewisite (2,3-dimercaprol; BAL) has been used for the treatment of poisoning by arsenic compounds[36], but this compound has many disadvantages such as a low safety ratio, unpleasant side effects and difficulty in systemic administration. Two recent reports have indicated in animal models that treatment with meso 2,3-dimercaptosuccinic acid (DMSA) and sodium 2,3-dimercaptopropane 1-sulfonate (DMPS) may reverse most of the immunosuppressive effects[37, 38]. Attempts are also being made in our laboratory to synthesise and evaluate mono and diesters of DMSA for treating chronic low level GaAs exposure. Preliminary results indicate a beneficial role of monoisoamyl DMSA in treating GaAs exposure (Flora *et al*. unpublished results). Another possible approach to chelation treatment is combination therapy with an essential metal or an antioxidant as an adjuvant during chelating agent administration. We recently reported that selenium administration during GaAs exposure has some preventive value particularly against the altered immunological and haematopoietic effects[39]. In a first study of its kind we also reported that combined administration of N-acetyl cystein during treatment with meso 2,3-dimercaptosuccinic acid (DMSA) leads to a more pronounced elimination of arsenic from the soft tissues and recovery in the altered biochemical variables indicative of oxidative stress[40], but these data are only from experimental models and not supported by evidence in any human case study.

Future Research Trends

Further research is urgently required in the following important areas:

- —There is a need to develop biological indicators that are useful, more specific and reliable under conditions of multielement exposure.
- —There is a need to understand the mechanism and metabolism of action of cell injury so that the indicator response can be correctly interpreted.
- —It is also of great importance to investigate the role of various factors such as age, sex, physiological states, such as pregnancy, and nutritional status, which may influence the toxic manifestation of these intermetallic compounds.
- —Lastly, there is an urgent need to develop safe, highly effective and specific antidotes for treating cases of possible acute or chronic GaAs/InAs exposure.

Conclusion

As is evident from the few above mentioned studies, these intermetallic semiconductor materials possess toxic biological properties and this may lead to potential occupational and environmental health consequences. Therefore, in order to prevent such hazards associated with the handling of these compounds, detailed studies need to be conducted in several areas viz. target organ toxicity, mechanisms of action, specific biological indicators, preventive and therapeutic measures, besides possible health monitoring of subjects handling these compounds.

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