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REVIEW PAPER

Toxicology of Gallium Arsenide: An Appraisal

S.J.S. Flora and S. Das Gupta

Division of Pharmacology and Toxicology
Defence Research & Development Establishment, Gwalior – 474 002

ABSTRACT

The toxicity of gallium arsenide (*GaAs*), a compound extensively used in Defence as a superior semiconductor material, in ground-and space-based radar and in electronic warfare is not well known. Results from recent reports on experimental animals indicate that *GaAs* produces profound effects on the lung, liver, immune and haematopoietic systems. *GaAs* is found to be soluble in aqueous solution and forms unidentified gallium and arsenic species upon dissolution. Different species of arsenic which are formed following the exposure may lead to various toxic effects. This paper gives a comprehensive account of work carried out in the toxicology of *GaAs*.

1. INTRODUCTION

Gallium arsenide (*GaAs*) is a group IIIa-Va intermetallic semiconductor that possesses superior electronic and optical properties as compared to those of the semiconductor silicon which is more commonly used in the electronic industry. *GaAs* is used in electronic industry primarily in the manufacture of transistors and light emitting diodes. Recently, *GaAs* is finding extensive use in Defence electronic equipments particularly as a superior semiconductor material. Microcircuits that utilise *GaAs* offer the distinct advantage of increased electron velocity which has led to the development of high frequency microwave and millimeter wave communications systems and ultrafast supercomputers. It is also a popular semiconductor material for the solar cells. Wide range of other uses for *GaAs* include satellite communication, electronic warfare (jammers and decoys) and intelligence warfare[1].

Exposure to airborne particulates of *GaAs* may be potential health hazards in the semiconductor industry. Assessment of risk to these workers from *GaAs* exposure is complicated due to the lack of toxicity data available for this compound. Toxicology of *GaAs* is mainly regulated on the basis of inorganic arsenic toxicity data. However, it has recently been reported that *GaAs* dissociates into its constitutive moieties both *in vitro* and *in vivo* following intratracheal or oral instillation[2]. It is generally accepted that gallium compounds are of low toxicity[3] while inorganic arsenic compounds are known to be very toxic. *GaAs* and gallium oxide (Ga_2O_3) have been shown to be pneumotoxicants which alter various pulmonary biochemical and morphological variables following intratracheal administration in rats[4,5]. Toxicity of gallium compounds have mainly three characteristic features: (i) species variation is wide; the toxicity for larger species being more than for the smaller, (ii) intravenous administration of the compound is more toxic than the subcutaneous route while soluble gallium salts by oral intake are practically non toxic, and (iii) cumulative toxicity is marked.

Lethal or near sub-lethal doses in experimental animals (dogs) provoked vomiting, diarrehoea, anorexia and weight loss soon after the injection. Urine samples contained red blood corpuscles (RBC) and albumin. In some animals the haemoglobin values were reduced[3].

2. METABOLISM OF *GaAs*

Gallium arsenide is soluble in various media and when administered orally it is mostly excreted in the

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faeces while in the urine it is scanty. The compound, when administered intraperitoneally, is poorly excreted in both faeces and urine[6]. *GaAs* has been shown to dissolve *in vivo* and the released arsenic species were metabolised as other inorganic arsenic and were found in the urine and tissues. Webb *et al*[2] reported that a large amount of arsenic was taken up by the blood. It is well known that arsenic has a great affinity for the red blood cells of the rats which persists for a long period[8,9]. However, Yamamuchi *et al*[6] reported that oral administration of *GaAs* resulted into low arsenic concentration in blood and its rapid disappearance there from. The obvious discrepancy between these findings could be attributed to the difference in the species of animals used.

LD_{50} of gallium arsenide is reported to be 4.7 g/kg by Roschina[9] and it shows that *GaAs* is less toxic than inorganic arsenic compounds which may be due to its low solubility. A portion of the arsenic dissociates from *GaAs* and acts as inorganic arsenic and therefore, it is hazardous to take the toxicity of *GaAs* lightly.

3. TOXIC MANIFESTATION IN HUMANS

A single case of industrial gallium poisoning represents the only reported instance. In a 43-year old woman, exposure to GaF_3 fumes resulted in skin rashes of the hand within 24 hours with neurological sequelae and after few days, it was diagnosed as mild radial palsy with muscle weakness. The rash cleared in two weeks but the pain and weakness persisted for three months.

Clinical studies in humans with stable ^{72}Ga have been carried out. Dermatological manifestations appeared. Haematological changes like, the decrease in total leukocytes has been observed. Gastrointestinal symptoms have also been noted[10]. Deterioration of health hazards caused by occupational exposure to inorganic arsenic has been seen in workers at copper smelters and at arsenic trioxide and arsenic agrochemical plants. Because of changes in industrial structure in recent years, the use of arsenic compounds has been on the increase. *GaAs* semiconductor has the advantage of operations at a higher speed than the silicon semiconductor.

Actual status of gallium or arsenic exposure of *GaAs* plant workers and deterioration of their health is not very well known. In an extensive study done Yamamuchi *et al*[11] established 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 and copper smelter workers. It was revealed that total arsenic concentration in the hair of all groups of *GaAs* plant workers tended to be higher than the control groups.

4. EFFECTS ON HAEM SYNTHESIS

A schematic presentation of the haem synthesis is shown in Fig. 1. Atleast one step in haem synthesis may be affected by *GaAs*[12,13] δ-aminolevulinic acid dehydratase (ALAD) is probably the enzyme in the haem pathway that is most sensitive to *GaAs*. Inhibition of this enzyme in the haem pathway blocks the utilisation of δ-aminolevulinic acid (ALA) and in subsequent decline in haem synthesis. Data by Goering *et al*[12] suggest that *Ga* is the primary inhibitor of ALAD following dissolution of *GaAs in vivo* and that competition for or displacement of zinc from the enzymes active site may be responsible for inhibition. Our studies in experimental animals have also shown that single exposure to *GaAs* produced a dose dependent inhibition of blood ALAD activity at various

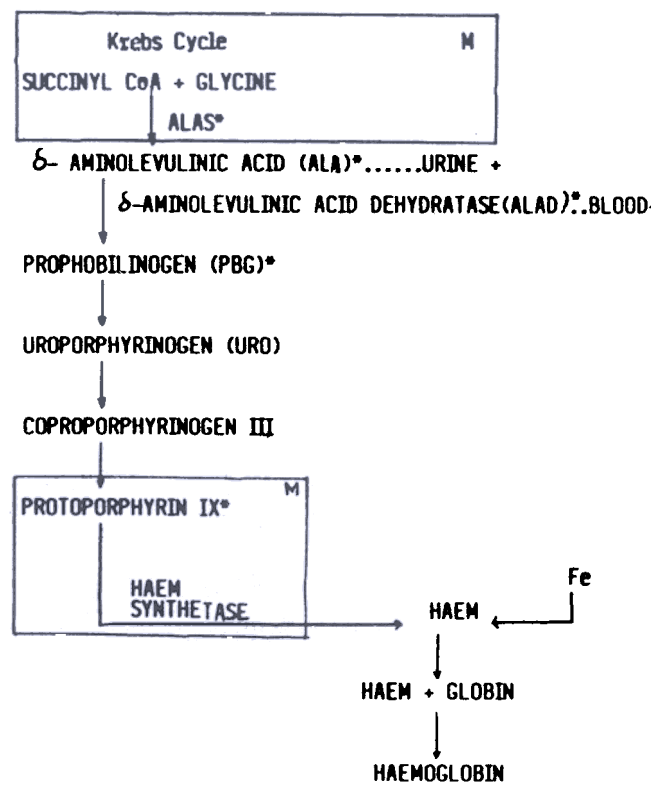

Figure 1. Schematic diagram of haem synthesis pathway (* denotes possible sites of *GaAs* expoure, M denotes mitochondria).

time interval (day 1,7 and 15) following exposure[13] Inhibition of ALAD was also observed in hepatic and brain tissues after single exposure to 1000 and 2000 mg/kg *GaAs*. Levels of blood zinc protoporphyrin and urinary ALA excretion were also found to be significantly elevated indicating a disturbance in the haem synthesis pathway following *GaAs* exposure. Blood *As* contents increased significantly in dose dependent manner however, blood *Ga* contents were not detectable in normal controls or 500 mg *GaAs*-administered rats. However, it increased significantly in animals which were given higher doses of *GaAs*. Interestingly, the inhibition of blood ALAD was also prominent in animals receiving higher dose of *GaAs* indicating that the *Ga* probably is the true inhibitor of ALAD in *GaAs*[13]. The measurement of haem precursor, ALA in urine, coupled with the assay of RBC ALAD activity may be of value as an early indicator of *GaAs* exposure and/or toxicity.

5. PULMONARY TOXICITY OF *GaAs*

In industry, the major route of exposure is via the inhalation of air borne particles during the production of *GaAs* and the wafer processing. Toxicological studies in rat[2] and mice[13] have shown that intratracheal administration of *GaAs* produces its major adverse effect on the lung. In rats, a single 100 mg/kg dose of GaAs led to an inflammatory response in the lung and pneumonocytic hyperplasia. Total lung contents of lipids, protein and DNA were significantly increased. Systemic alterations include body weight decrease and porphyrin increase in exposed rats. In mice, the primary histopathological changes in the lung was the appearance of consolidated areas consisting of granular basophilic material in the alveolar spaces. A hyperplastic response was not evident in the lung. A cellular response to *GaAs* was seen in the lung with an increase in macrophages and to a lesser extent polymorphonuclear leukocytes. Webb *et al*[5] confirmed that significantly smaller fraction of *GaAs* is a relatively more severe pneumotoxicant which decreased the particle mean count and mean volume diameter to 1.63 m and 5.82 m respectively, increased the *in vivo* dissolution rate of *GaAs*, increased the severity of pulmonary lesions previously associated with *GaAs* exposure and resulted in unique pathological sequalae in affected lung tissues. Pulmonary fibrosis as indicated by the analysis of 4-hydroxyproline contents of the lung was not considered statistically significant although, histopathological examination of lung tissues revealed a mild fibrotic response. This study provided additional information that pulmonary exposure to respirable *GaAs* is a potential health hazard in the semiconductor industry.

6. IMMUNOTOXIC EFFECTS OF *GaAs*

Like many other metals and metallic compounds, *GaAs* has been shown to alter several inmmune responses. Immunotoxic potential of *GaAs* following pulmonary exposure has been reported by Sikorski *et al*[14] and McCay *et al*[15]. They suggested that *GaAs* reduced the *in vivo* splenic *IgM* antibody forming cell response to sheep RBC by 66 per cent at higher dose. *GaAs* was also shown to impair the ability of murine system to protect against *B*16 *F*10 tumour challenge. Recently, Sikorski *et al*[16,17] further demonstrated that *GaAs* exposure results in a dose related suppression of the primary antibody response to sheep RBC. The adherent population (primarily macrophages), T cell and B cell are all affected by *GaAs* exposure to a similar degree, indicating the potential for a similar mechanism of toxicity in these cells. It was also observed that pulmonary exposure to *GaAs* adversely affects certain parameters of both humoral and cell mediated immunity (CMI). Investigation of alterations in specific immune functions seen *in vivo* and *in vitro* coupled with host resistance studies aids in identification of the immune defect that occurs. A report by Burns *et al*[18] suggested that all the cells involved in the generation of primary immune response are effected to a similar degree by *GaAs*. Further, it was concluded that arsenic does not appear to be the sole toxic component of *GaAs*. The arsenic that dissociates from *GaAs*, however, may be responsible for some of the immunotoxic effects and may constitute a potential risk to workers exposed to this compound.

7. HEPATOTOXIC EFFECTS OF *GaAs*

Webb *et al*[2] reported impaired liver function due to the arsenic dissociated from *GaAs* as an increased urinary excretion of uroporphyrin following oral exposure to arsenic and also from animal experiments. It is known that inorganic arsenic compounds are slightly hepatotoxic[19,20]

8. DETECTION AND EARLY BIOCHEMICAL MARKERS

The haem-biosynthetic pathway has proven extensively useful in the development of early biological indicators of exposure to organic and inorganic toxicants. Webb *et al*[2] reported that exposure of rats to *GaAs* elevated the uroporphyrin and coproporphyrin ratio in urine but a biological indicator for the gallium moiety of this compound has not been reported. Goering *et al*[12] suggested that altered urinary excretion pattern of ALA plus assay of RBC ALAD activity may be of potential value as early biological indicators of exposure to *GaAs*. Recently, the authors also confirmed the findings of Goering *et al*[12] but it was observed that the decrease in blood ALAD activity has not consistently been accompanied with urinary ALA excretion[13]. It was concluded that more specific and sensitive indicators of *GaAs* exposure/toxicity need to be evaluated including perturbation of haem-biosynthesis and haemoprotein function in target tissues.

9. PREVENTIVE MEASURES

As a general principle *GaAs* processes must be conducted in a carefully controlled manner to protect the health of the workers. Well known industrial hygiene principles like local exhaust ventilation, careful house keeping, selected work procedures, etc. should be employed in achieving this. If all these mechanisms operated ideally, *GaAs* in the environment would be controlled. However, there is some risk of employees being exposed to greater than recommended arsenic concentration. Therefore, there is need for a type of protection that may be thought of as secondary control. Respiratory protection devices, company issued work clothes, gloves and facilities furnished in support of personnel hygiene are in this category. Air monitoring should be performed periodically to determine whether the exposures to *GaAs* are within limit.

10. TREATMENT

As the toxicology of *GaAs* is still not very well understood and clearly defined, the treatment also remains to be elucidated. But as discussed, *GaAs* dissociates into its constituent moieties, the gallium and arsenic *in vivo*, the toxicity of *GaAs* should not be taken lightly particularly because of the well defined toxicity of arsenic. For many years British anti lewisite (BAL, also commonly known as dimercaprol) has been used for the treatment of poisoning by compounds of arsenic[21]. BAL however, suffers the disadvantage of a low safety ratio, unpleasant side effects and difficulty in systemic administration. The current recommended treatment schedule for arsenic poisoning for humans is 20 μmol/kg given four times at an interval of 4 hours on the first day, followed by two doses per day until recovery[22]. The chemically related analogues of dimercaprol, meso 2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercaprol propane 1-sulphonate (DMPS) are more water soluble, orally active and markedly less toxic compounds to BAL[23]. They have although, not yet been tested in detail for arsenic or *GaAs* toxicity. But they appear promising on the basis of data from a few animal studies available[24,25]. Further studies are required to evaluate the efficacy of DMSA and DMPS as replacement drugs for BAL for the treatment of arsenic and possibly *GaAs* exposure.

11. CONCLUSION

Little is known about the toxicity of *GaAs* at present. The results from a few isolated reports suggest the need for in depth studies with *GaAs* to determine the level of gallium and arsenic in extrapulmonary tissues viz., the liver, kidney and brain following prolonged inhalation or oral exposure to this compound. Further, specific and sensitive indicators of *GaAs* exposure/toxicity need to be evaluated including perturbation of haem-biosynthesis.

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