GALLIUM ARSENIDE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 1303-00-0
Deleted CAS Reg. No.: 12254-95-4, 106495-92-5, 116443-03-9, 385800-12-4
Chem. Abstr. Serv. Name: Gallium arsenide (GaAs)
IUPAC Systematic Name: Gallium arsenide
Synonyms: Gallium monoarsenide

1.1.2 *Molecular formula and relative molecular mass*

GaAs Relative molecular mass: 144.6

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Grey, cubic crystals (Lide, 2003)
(*b*) *Melting-point*: 1238 °C (Lide, 2003)
(*c*) *Density*: 5.3176 g/cm^3 (Lide, 2003)
(*d*) *Solubility*: Insoluble in water (Wafer Technology Ltd, 1997); slightly soluble in 0.1 M phosphate buffer at pH 7.4 (Webb *et al*., 1984)
(*e*) *Stability*: Decomposes with evolution of arsenic vapour at temperatures above 480 °C (Wafer Technology Ltd, 1997)
(*f*) *Reactivity*: Reacts with strong acid reducing agents to produce arsine gas (Wafer Technology Ltd, 1997)

1.1.4 *Technical products and impurities*

Purity requirements for the raw materials used to produce gallium arsenide are stringent. For optoelectronic devices (light-emitting diodes (LEDs), laser diodes, photo-detectors, solar cells), the gallium and arsenic must be at least 99.9999% pure; for

integrated circuits, a purity of 99.99999% is required. These purity levels are referred to by several names: 99.9999%-pure gallium is often called 6-nines, 6N or optoelectronic grade, while 99.99999%-pure gallium is called 7-nines, 7N, semi-insulating (SI) or integrated circuit (IC) grade.

For 7N gallium, the total of the impurities must be < 100 µg/kg. In addition to the challenge of consistently producing material with such high purity, there are difficulties in detecting the small quantity of impurities. Certain impurities cause more problems than others during gallium arsenide production. Those of most concern are calcium, carbon, copper, iron, magnesium, manganese, nickel, selenium, silicon, sulfur, tellurium and tin. Generally, these elements should be present in concentrations < 1 µg/kg in both the gallium and the arsenic. Lead, mercury and zinc should be present in concentrations < 5 µg/kg. Although aluminum, chlorine and sodium are often present, the concentrations of each should be < 10 µg/kg (Kramer, 1988). Some companies have even more stringent requirements (Recapture Metals, 2003).

1.1.5 *Analysis*

The monitoring of occupational exposure to gallium arsenide can only be based on measurements of arsenic or gallium concentrations in workplace air or in human tissues or body fluids (biological monitoring), because there is no analytical method capable of measuring gallium arsenide per se in the above media.

(*a*) *Determination of gallium*

Monitoring of exposure to gallium arsenide by determination of gallium has so far not been used due to the limited availability of analytical methods with sufficiently low detection limits.

Instrumental neutron activation analysis (INAA) has been employed successfully for the determination of gallium in ambient air (Kucera *et al*., 1999) and can therefore be used for the determination of gallium in workplace air. A newly developed Mist-UV sampling system coupled with ICP–MS analysis allows the determination of volatile gallium compounds in the atmosphere (Ito & Shooter, 2002).

Several methods have been designed and tested for the determination of gallium in biological materials, mainly in the analysis of spiked samples. These include spectrophotometry (Beltrán Lucena *et al*., 1994), fluorescence spectrometry (Requena *et al*., 1983; Afonso *et al*,. 1985; Ureña *et al*., 1985; Ureña Pozo *et al*., 1987; Cano Pavón *et al*., 1988; Salgado *et al*., 1988; Cano Pavón *et al*., 1990; Sanchez Rojas & Cano Pavón, 1995), electrothermal AAS (Nakamura *et al*., 1982; Ma *et al*., 1999) and F-AAS with preconcentration (Anthemidis *et al*., 2003).

Data on gallium concentrations in human tissues and body fluids are scarce. Scansetti (1992) reported a mean blood concentration in healthy donors of 3 µg/L.

(*b*) *Determination of arsenic*

Until now, only measurements of arsenic have been used for monitoring exposure to gallium arsenide because occupational exposure limits for arsenic have been established in many countries and the analytical methods available for its determination are more sensitive than those for gallium.

(i) *Workplace air monitoring*

Yamauchi *et al*. (1989) measured arsenic concentrations in air in gallium-arsenide plants using a method similar to those used to determine inorganic arsenic in workplace air (Hakala & Pyy, 1995; Jakubowski *et al*., 1998; Apostoli *et al*., 1999). Airborne respirable particulate matter is collected by drawing air into a stationary or personal sampler through a membrane filter made of polycarbonate, cellulose ester and/or teflon. The filter containing the collected air particulates is digested in various concentrated mineral acids (chlorhydric acid, nitric acid, sulfuric acid, perchloric acid) or a mixture thereof and the arsenic concentration in the digest is determined by hydride generation AAS (Hakala & Pyy, 1995; Jakubowski *et al*., 1998) or ICP-MS (Apostoli *et al*., 1999). Non-destructive determination of the arsenic content on a filter can also be achieved using INAA, with a detection limit of about 0.5 ng/m^3 (Kucera *et al*., 1999).

(ii) *Biological monitoring*

Preliminary considerations

Biomonitoring of exposure to gallium arsenide by measuring arsenic in human tissues or body fluids has several limitations. Firstly, gallium arsenide has a low solubility and is poorly absorbed in the gastrointestinal tract, resulting in rapid elimination of the compound in the faeces (Webb *et al.*, 1984; Yamauchi *et al.*, 1986) (see also Section 4.1.2). Secondly, determining the total concentration of arsenic in body fluids, e.g. in urine, is not an optimum measure of occupational exposure to arsenic. Gallium arsenide is partly dissociated *in vivo* into inorganic arsenic and gallium (Webb *et al.*, 1984; Yamauchi *et al.*, 1986). Inorganic arsenic is methylated in the human body to monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V), which are readily excreted in urine (Vahter, 2002). However, arsenic in seafood is present predominantly in the forms of arsenobetaine and arsenocholine, which do not undergo biotransformation and are also excreted in urine (Apostoli *et al*., 1999; Vahter, 2002). Hence, the concentration of total arsenic in body fluids is dependent on the concentration and the species of dietary arsenic. Therefore, it is preferable to use speciation analysis in biomonitoring of arsenic exposure; alternatively, subjects enrolled in occupational health studies should refrain from consuming seafood for a couple of days before the analysis of their body fluids.

Similarly, determination of arsenic concentration in hair is associated with the problem of distinguishing external contamination from the endogenous content of arsenic in this tissue (Yamauchi *et al*., 1989).

Analytical methods

Numerous methods (reviewed recently in IARC, 2004) are available for the determination of the total concentration of arsenic and its species in blood, serum, urine and other biological materials. The methods most commonly used include electrothermal AAS, AAS with hydride generation, ICP-AES, ICP-MS, atomic fluorescence spectrometry (AFS) and INAA. The advantages and shortcomings of these and other less frequently used techniques, such as spectrophotometric and electroanalytical methods, have been reviewed comprehensively (Burguera & Burguera, 1997; IARC, 2004). The analytical methods used for arsenic speciation are based on the combination of a powerful separation process and an adequate element-specific detection, using so-called hyphenated analytical techniques. The methods most frequently employed for separation and preconcentration involve solvent extraction, including solid-phase extraction (Yalcin & Le, 2001; Yu *et al*., 2003), precipitation and coprecipitation, ion-exchange chromatography (IEC), capillary electrophoresis (Greschonig *et al*., 1998), gas chromatography and high-performance liquid chromatography (HPLC). The element-specific detection is performed using the same analytical techniques as for determination of total arsenic. On-line coupling of some separation techniques, usually HPLC or IEC, with the most sensitive detection methods (AAS, AFS, ICP-AES, ICP-MS) is frequently used. A detection limit at the nanogram level has been achieved by AAS coupled with hydride generation before detection (Burguera & Burguera, 1997).

(iii) *Reference values for occupationally non-exposed populations*

Concentrations of total arsenic found in human blood, serum, plasma and urine have been reviewed (Iyengar *et al*., 1978; Versieck & Cornelis, 1980; Heydorn, 1984; Iyengar & Woittiez, 1988). The data suggest that there are regional differences and short-term effects of dietary intake, especially seafood. After exclusion of values suspected of such variations, the following median reference values were given: whole blood, 5 μg/L (Iyengar & Woittiez, 1988); serum or plasma, 1–3.5 μg/L (Heydorn, 1984; Iyengar & Woittiez, 1988); and urine, 20 μg/L (Iyengar & Woittiez, 1988). The data available for the individual arsenic species are still insufficient to make reliable estimates of reference values, presumably because of methodological problems.

1.2 Production and use

1.2.1 *Production*

Gallium occurs in very small concentrations in many rocks and ores of other metals. Most gallium is produced as a by-product of processing bauxite, and the remainder is produced from zinc-processing residues. Only part of the gallium present in bauxite and zinc ores is recoverable, and the factors controlling the recovery are proprietary. Therefore, an estimate of current reserves cannot be made. The world bauxite reserve base is so large

that much of it will not be mined for many decades; hence, most of the gallium in the bauxite reserve base cannot be considered to be available in the short term (Kramer, 2003).

Estimates of primary production of gallium in the world between 1995 and 2002 have varied between 35 and 100 tonnes. In 2003, about 64 tonnes were produced, with China, Germany, Japan and the Russian Federation being the major producers; countries with smaller output included Hungary, Kazakhstan, Slovakia and the Ukraine. Refined gallium production in 2003 was estimated to be about 83 tonnes, including some scrap refining. France was the largest producer of refined gallium, using crude gallium produced in Germany as feed material. Japan and the USA are two other large gallium-refining countries (Kramer, 1996–2004).

Demand for gallium in the USA in 2003 was satisfied by imports, mainly low-purity material from China, Kazakhstan and the Russian Federation and smaller amounts of high-purity material from France. In addition, in 2002, the USA imported an estimated 120 tonnes of doped and undoped gallium arsenide wafers, mainly from Finland, Germany, Italy and Japan (Kramer, 2002, 2003).

Consumption of high-purity gallium in Japan in 2002 was estimated to be 108 tonnes, including domestic production of 8 tonnes, imports of 55 tonnes and scrap recycling of 45 tonnes (Kramer, 2003).

The technology of gallium arsenide processing has been reviewed in detail (Harrison, 1986; Kitsunai & Yuki, 1994). Gallium arsenide can be obtained by direct combination of the elements at high temperature and pressure; it can also be prepared, mainly as a thin film, by numerous exchange reactions in the vapour phase (Sabot & Lauvray, 1994).

Gallium arsenide single crystals are more difficult to fabricate than those of silicon. With silicon, only one component needs to be controlled, whereas with gallium arsenide, a 1:1 ratio of gallium atoms to arsenic atoms must be maintained. At the same time, arsenic volatilizes at the temperatures needed to grow crystals. To prevent loss of arsenic, which would result in the formation of an undesirable gallium-rich crystal, gallium arsenide single-crystal ingots are grown in an enclosed environment. Two basic methods are used to fabricate gallium arsenide ingots: the boat-growth, horizontal Bridgeman or gradient-freeze technique and the liquid-encapsulated Czochralski technique. Ingots produced by the horizontal Bridgeman method are D-shaped and have a typical cross-sectional area of about 2 in^2 [13 cm^2]. In contrast, single-crystal ingots grown by the liquid-encapsulated Czochralski method are round and are generally 3 in [7.5 cm] in diameter, with a cross-sectional area of about 7 in^2 [45 cm^2] (Kramer, 1988; Kitsunai & Yuki, 1994). Ingots grown by the horizontal Bridgeman method are cleaned in chemical baths of aqua regia and isopropyl alcohol, and sandblasted using an abrasive material such as silicon carbide or calcined alumina.

The crystalline orientation of the gallium arsenide ingot is checked by X-ray diffraction and the ends are cut off with a diamond blade saw. The ingots are shaped by grinding the edges and then sliced into wafers along the proper crystalline axis. Wafers pass through several stages of surface preparation, polishing and testing before they are ready for device manufacture or epitaxial growth. [Epitaxy is a method for growing single crystals in which

chemical reactions produce thin layers of materials whose lattice structures are identical to that of the substrate on which they are deposited.] Pure gallium arsenide is semi-insulating and, in order to conduct electricity, a small number of atoms of another element must be incorporated into the crystal structure; this is called doping. Doping is accomplished by either ion implantation or epitaxial growth (Harrison, 1986; Kramer, 1988).

Because of the low yield in processing gallium arsenide for optoelectronic devices or integrated circuits, substantial quantities of scrap are generated during the various processing stages. This scrap has varying gallium (from < 1 to 99.99%) and impurity contents, depending on the processing step from which it results. In processing gallium arsenide scrap, the material is crushed, if necessary, and then dissolved in a hot acidic solution. This acidic solution is neutralized with a caustic solution to precipitate the gallium as gallium hydroxide, which is filtered from the solution and washed. The gallium hydroxide filter cake is redissolved in a caustic solution and electrolysed to recover 3N to 4N gallium metal. This metal may be refined to 6N or 7N gallium by conventional purification techniques (Kramer, 1988).

Available information indicates that gallium arsenide is produced by three companies in Taiwan, China, two companies in Japan, and one company each in China, the Ukraine and the USA (Chemical Information Services, 2003).

1.2.2 *Use*

Gallium arsenide has light-emitting properties, high electron mobility, electromagnetic properties and photovoltaic properties. As a semiconductor, it has several unique material properties which can be utilized in high speed semi-conductor devices, high power microwave and millimetre-wave devices, and optoelectronic devices including fibreoptic sources and detectors. Its advantages as a material for high speed devices are high electron mobility and saturation velocity, and relatively easy growth of semi-insulating substrates which render low parasitics and good device isolation. Other useful properties are controllable band gap by alloying, desirable ionization and optical absorption properties. Gallium arsenide has certain advantages over other semiconductor materials: (1) faster operation with lower power consumption, (2) better resistance to radiation and, most importantly, (3) it may be used to convert electrical into optical signals (Chakrabarti, 1992; Greber, 2003).

In 2002, more than 95% of gallium consumed in the USA was in the form of gallium arsenide for optoelectronic devices and integrated circuits. Analogue ICs were the largest single application for gallium, representing 65% of gallium demand (Kramer, 2003). ICs are used in defence applications, high-performance computers and telecommunications. The developments in gallium arsenide IC technology have been reviewed (Welch *et al*., 1985; Chakrabarti, 1992). About 34% of the gallium consumed was used in optoelectronic devices, which include LEDs, laser diodes, photodetectors and solar cells. Optoelectronic devices are used in applications such as aerospace, consumer goods, industrial components,

medical equipment and telecommunications. The remaining 1% was used in research and development, specialty alloys and other applications (Kramer, 2003).

Many manufacturers have introduced new LEDs based on gallium arsenide technology which offer improvements over current LEDs. In many cases, the new LEDs are brighter, last longer and/or can be used in new applications (Kramer, 2002).

Gallium arsenide wafer manufacturers and some electrical companies produce gallium arsenide epitaxial-growth wafers and LED drips. Vapour-phase epitaxy or liquid-phase epitaxy is used to grow gallium arsenide layers for most LEDs. The super-bright red LEDs are manufactured using liquid-phase epitaxy to grow aluminum–gallium–arsenide on gallium arsenide substrates. Epitaxial growth based on metal–organic chemical vapour deposition (MOCVD) technology is used in manufacturing some types of infrared LEDs used in optocouplers. MOCVD is also used to grow a gallium arsenide layer (buffer layer) on gallium arsenide substrates for low-cost optic fibres dedicated to local area computer networks. Gallium arsenide-based laser diodes are manufactured using liquid-phase epitaxy, MOCVD and molecular beam epitaxy technologies (Kitsunai & Yuki, 1994; Sabot & Lauvray, 1994).

For analogue ICs, the requirements for epitaxy grow at the same rate as frequencies increase. An epitaxial gallium arsenide layer is also required for most microwave devices with frequencies over 20 GHz. Photovoltaic applications require gallium arsenide wafers and epitaxial layers. Night-vision system devices use an epitaxial layer of gallium arsenide applied to one end of a photomultiplier to enhance infrared images. Gallium arsenide epitaxial-growth wafers are is also used in optical ICs and magnetoelectric transducers (Sabot & Lauvray, 1994).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Gallium arsenide does not occur naturally. Gallium is present in the earth's crust at 5–15 mg/kg and is recovered as a by-product of the extraction of aluminum and zinc from their ores (Beliles, 1994; Sabot & Lauvray, 1994).

Arsenic concentration in the earth's crust is generally < 2 mg/kg, but may be elevated in zones of active or extinct volcanic activity (IARC, 2004).

1.3.2 *Occupational exposure*

Exposure to gallium arsenide occurs predominantly in the microelectronics industry where workers are involved in the production of gallium arsenide crystals, ingots and wafers, in grinding and sawing operations, in device fabrication, and in sandblasting and clean-up activities (Webb *et al.*, 1984; Harrison, 1986). The National Institute for Occupational Safety and Health (NIOSH) estimated that in 1981 the microelectronics industry

employed approximately 180 000 workers in the USA, with over 500 plants manufacturing semiconductors (National Institute for Occupational Safety and Health, 1985).

Exposure to gallium arsenide can only be monitored by determining arsenic concentrations. Several reports describe the assessment of exposure to arsenic during gallium arsenide production and use (Harrison, 1986; Yamauchi *et al*., 1989; Sheehy & Jones, 1993). Harrison (1986) reported short-term exposure concentrations of arsenic measured at two facilities during epitaxial vacuum servicing and beadblasting of 0.29 and 2.5 mg/m^3, respectively.

Sheehy and Jones (1993) conducted more thorough workplace assessments of total arsenic exposure during 1986–87 by collecting personal breathing zone and workplace air samples at various stages of gallium arsenide production in three different plants. In areas where arsine gas was used, arsine concentrations were also measured. In general, arsenic concentrations in air in personal breathing zones were found to be < 5 μg/m^3 in each of the three plants. However, concentrations in air samples collected from personal breathing zones of individuals responsible for cleaning activities in the crystal-growth area were as high as 2.7 mg/m^3. Wipe samples collected from various work sites showed mean concentrations up to 970 μg/100 cm^2. The authors noted that in two of the three plants monitored, 30–70% of the arsenic collected in air in personal breathing zones passed through the filters and was collected on charcoal tubes, implying that a large portion of the exposure to arsenic was due to arsine gas. The authors concluded that in order to determine exposure to arsenic during gallium arsenide production, both particulate and gaseous arsenic should be monitored.

Yamauchi *et al*. (1989) measured inorganic arsenic, MMA^V, DMA^V and trimethylarsenic compounds in the urine and hair of workers involved in various stages of gallium arsenide crystal and wafer production. Total arsenic concentration in workplace air ranged from 2 to 24 μg/m^3. For workers in these areas, the mean concentration of total arsenic in hair was significantly greater than that in the controls and ranged from 1.11 to 6.28 μg arsenic per g of hair, with inorganic arsenic contributing 85–99.6% of total arsenic. [The Working Group noted discrepancies between the means and ranges of concentrations of arsenic species in hair, and between text and table in the percentage of inorganic arsenic over total arsenic.] There was no difference in DMA^V concentrations in hair between workers and controls (approximately 0.03 μg/g arsenic), and MMA^V and trimethylarsenic compounds were not detected in either group. Of the arsenic species detected in urine, trimethylarsenic compounds were the most abundant, followed by DMA^V, inorganic arsenic and MMA^V. There was no difference between pre- and postwork concentrations for any of the arsenic species analysed. The authors suggested that the high concentrations observed were possibly due to the high consumption of seafood containing arsenic (arsenobetaine and arsenocholine) by workers in Japan. They concluded that urinary arsenic could be used as a biomarker of exposure only if speciation analyses are performed (see also Section 1.1.5(*b*)(ii)); determination of arsenic in hair, on the other hand, was suggested for environmental monitoring of arsenic.

A study was conducted to examine the relationship between total arsenic concentrations in hair of employees in a semiconductor fabrication facility and their job responsibility (de Peyster & Silvers, 1995). Airborne arsenic was found in areas where equipment was cleaned but not in administrative areas. The highest arsenic concentration found in the study (15 μg/m^3) was in an air sample collected over a period of 2 h in the breathing zone of an employee cleaning a source housing in an area with local exhaust ventilation. A concentration of 2 μg/m^3 was found during the remainder of the cleaning period (~53 min). Maintenance workers who were regularly assigned to cleaning equipment, and therefore presumed to have the highest potential exposure, had a mean concentration of arsenic in hair of 0.042 μg/g. This was slightly higher than the mean of 0.033 μg/g observed in controls working in administrative areas, but the difference was not statistically significant. Maintenance workers who only occasionally cleaned and maintained arsenic-contaminated equipment had a mean arsenic concentration in hair of 0.034 μg/g. The highest mean concentration of arsenic in hair, 0.044 μg/g, was found in the group of supervisors and engineers. However, the highest concentrations in this group (0.076 and 0.106 μg/g) were observed in two heavy smokers. When smokers were eliminated from the analysis, means increased according to levels of presumed occupational exposure. Sex, tap-water consumption and dietary habits may also have affected arsenic concentrations in hair.

1.4 Regulations and guidelines

The only occupational exposure limit for gallium arsenide in the available literature was reported by NIOSH. NIOSH recommended a ceiling value of 0.002 mg/m^3 for gallium arsenide (ACGIH Worldwide®, 2003). No occupational exposure limits have been set for gallium.

Occupational exposure limits and guidelines for arsenic in some countries are presented in Table 1. Regulations and guidelines for arsenic in drinking-water were summarized recently by IARC (IARC, 2004).

2. Studies of Cancer in Humans

See Introduction to the Monographs on Gallium Arsenide and Indium Phosphide.

Table 1. Occupational exposure limits and guidelines for arsenic (elemental and inorganic)

Country or region	Concentration (mg/m^3)	Interpretation[a]	Carcinogen classification
Australia	0.05	TWA	1[b]
Belgium	0.1	TWA	Ca[c]
Canada			
Alberta	0.2	TWA	
Quebec	0.6	STEL	
	0.1	TWA	
China	0.01	TWA	
	0.02	STEL	
Finland	0.01	TWA	
Germany		MAK	1[d]
Hong Kong SAR	0.01	TWA	A1[e]
Ireland	0.1	TWA	Ca1[f]
Japan	0.003	TWA	1[g]
Malaysia	0.01	TWA	
Netherlands	0.05	TWA	
	0.1	STEL	
New Zealand	0.05	TWA	A1[e]
Norway	0.01	TWA	Ca[h]
Poland	0.01	TWA	Rc[i]
South Africa	0.1	TWA	
Sweden	0.01 (new facilities or alteration of old ones)	TWA	Ca[j]
	0.03	TWA	Ca
UK	0.1	TWA (MEL)	
USA[l]			
ACGIH	0.01	TWA (TLV)	A1[e]
NIOSH	0.002	Ceiling (REL)	Ca[k]
OSHA	0.01	TWA (PEL)	Ca[k]

From ACGIH Worldwide® (2003)

[a] TWA, time-weighted average; STEL, short-term exposure limit; MAK, maximum allowed concentration; MEL, maximum exposure limit; TLV, threshold limit value; REL, recommended exposure limit; PEL, permissible exposure limit

[b] Established human carcinogen

[c] Carcinogen

[d] Substance which causes cancer in man

[e] Confirmed human carcinogen

[f] Substance known to be carcinogenic to humans

[g] Carcinogenic to humans

[h] Potential cancer-causing agent

[I] Agent carcinogen to humans

[j] Substance is carcinogenic.

[k] Carcinogen

[l] ACGIH, American Conference of Governmental Industrial Hygienists; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Health and Safety Administration

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

In a study undertaken by the National Toxicology Program (2000), groups of 50 male and 50 female B6C3F$_1$ mice, 6 weeks of age, were exposed by inhalation to gallium arsenide particulate (purity, > 98%; MMAD, 0.9–1.0 μm; GSD, 1.8–1.9 μm) at concentrations of 0, 0.1, 0.5 or 1 mg/m^3 for 6 h per day, 5 days per week, for 105 weeks (males) or 106 weeks (females). No adverse effects on survival were observed in exposed males or females compared with chamber controls (survival rates: 35/50 (control), 38/50 (low dose), 34/50 (mid dose) and 34/50 (high dose) in males and 36/50, 34/50, 31/50 or 29/50 in females, respectively; mean survival times: 687, 707, 684 or 701 days in males and 699, 699, 665 or 682 days in females, respectively). There was no evidence of carcinogenic activity in male or female mice exposed to gallium arsenide; however, exposure did result in the development of a spectrum of inflammatory and proliferative lesions of the respiratory tract of mice (National Toxicology Program, 2000) (see Section 4.3).

3.1.2 *Rat*

In a study undertaken by the National Toxicology Program (2000), groups of 50 male and 50 female Fischer 344/N rats, 6 weeks of age, were exposed by inhalation to gallium arsenide particulate (purity, > 98%; MMAD, 0.9–1.0 μm; GSD, 1.8–1.9 μm) at concentrations of 0, 0.01, 0.1 or 1 mg/m^3 for 6 h per day, 5 days per week, for 105 weeks. No adverse effects on survival were observed in treated males or females compared with chamber controls (survival rates: 13/50 (control), 13/50 (low dose), 15/50 (mid dose) and 13/50 (high dose) in males and 19/50, 17/50, 21/50 or 11/50 in females, respectively; mean survival times: 651, 627, 656 or 636 days in males and 666, 659, 644 or 626 days in females, respectively). Mean body weights were generally decreased in males exposed to the high dose throughout the study and slightly decreased in females exposed to the same dose during the second year compared with chamber controls. Although there was no evidence of carcinogenic activity in male rats exposed to gallium arsenide, exposure did result in the development of a spectrum of inflammatory and proliferative lesions of the respiratory tract (see Section 4.3). A clear neoplastic response was observed in the lung and the adrenal medulla of female rats. Increased incidence of mononuclear cell leukaemia was also observed. However, exposure to gallium arsenide did not cause an increased incidence of neoplasms in other tissues. The incidence of neoplasms and non-neoplastic lesions in female rats is reported in Table 2.

Table 2. Incidence of neoplasms and non-neoplastic lesions in female rats in a 2-year inhalation study of gallium arsenide

	No. of rats exposed to gallium arsenide at concentrations (mg/m^3) of			
	0 (chamber control)	0.01	0.1	1.0
Lung				
Total no. examined	50	50	50	50
No. with:				
Cyst, squamous	0	0	1 (4.0)	0
Hyperplasia, atypical	0	0	9[b] (2.2)	16[b] (2.2)
Inflammation, chronic active	11 (1.1)[a]	46[b] (1.5)	49[b] (2.8)	50[b] (3.7)
Metaplasia, squamous	0	0	2 (2.5)	1 (2.0)
Proteinosis	1 (1.0)	24[b] (1.0)	47[b] (2.2)	49[b] (3.8)
Alveolar epithelium, hyperplasia	14 (1.5)	9 (1.6)	17 (2.1)	14 (2.3)
Alveolar epithelium, metaplasia	0	1 (1.0)	36[b] (2.4)	41[b] (2.6)
Alveolar/bronchiolar adenoma				
Overall rate	0	0	2	7[b]
Alveolar/bronchiolar carcinoma				
Overall rate	0	0	2	3
Alveolar/bronchiolar adenoma or carcinoma				
Overall rate	0	0	4	9[b]
Squamous-cell carcinoma	0	0	0	1
Adrenal medulla				
Total no. examined	50	49	50	49
No. with:				
Hyperplasia	16 (2.0)	11 (1.8)	16 (1.8)	12 (2.5)
Benign pheochromocytoma	4	5	6	13[b]
Malignant pheochromocytoma	0	1	0	0
Mononuclear cell leukaemia				
Overall rate	22	21	18	33[c]

From National Toxicology Program (2000)

[a] Average severity grade of lesions in affected animals: 1, minimal; 2, mild; 3, moderate; 4, marked

[b] Significantly different ($p \leq 0.01$) from the chamber control group by the Poly-3 test

[c] Significantly different ($p \leq 0.05$) from the chamber control group by the Poly-3 test

In female rats, exposure to gallium arsenide caused a broad spectrum of proliferative, non-proliferative, and inflammatory lesions in the lungs, including a concentration-related increase in the incidence of alveolar/bronchiolar adenoma, and alveolar/bronchiolar adenoma and carcinoma (combined). Benign and malignant neoplasms of the lung

occurred in an exposure concentration-related manner in female rats. An increased incidence of atypical hyperplasia of the alveolar epithelium was observed in both male and female rats. Most lesions identified as atypical epithelial hyperplasia were irregular, often multiple, lesions that occurred at the edges of foci of chronic active inflammation. The incidence of alveolar epithelial metaplasia was significantly increased in females exposed to 0.1 or 1.0 mg/m^3 gallium arsenide. Alveolar epithelial metaplasia generally occurred within or adjacent to foci of chronic active inflammation and was characterized by replacement of normal alveolar epithelial cells (type I cells) with ciliated cuboidal to columnar epithelial cells. The incidences of chronic active inflammation and alveolar proteinosis were significantly increased in all exposed females, and severity of these lesions increased with increasing exposure concentration. Gallium arsenide particles were observed in the alveolar spaces and in macrophages, primarily in animals exposed to the higher concentrations.

Squamous metaplasia was present in a few gallium arsenide-exposed males and females and was usually associated with foci of chronic active inflammation. In one male in the high-dose group and one female in the mid-dose group, the squamous epithelium formed large cystic lesions diagnosed as squamous cysts. Although squamous epithelium is not a component of the normal lung, it often develops as a response to pulmonary injury associated with inhalation of irritants, especially particulates. One female in the high-dose group had an invasive squamous-cell carcinoma. The incidence of benign pheochromocytoma occurred in a dose-related manner in females and the incidence in females exposed to 1.0 mg/m^3 gallium arsenide was significantly increased compared to the chamber controls. Relative to chamber controls, the incidence of mononuclear cell leukaemia was significantly increased in females exposed to 1.0 mg/m^3. Mononuclear cell leukaemia is a common spontaneous neoplasm in Fischer 344/N rats and presents characteristically as a large granular lymphocytic leukaemia (National Toxicology Program, 2000).

3.2 Intratracheal instillation

Hamster

In a study by Ohyama and colleagues (1988), groups of 33 male 6-week old Syrian golden hamsters received weekly intratracheal instillations of 0 or 0.25 mg/animal gallium arsenide in 200 μL phosphate buffer [particle size and purity of vehicle not provided] for 15 weeks and were observed for 111–730 days. Gallium arsenide instillations significantly reduced survival (by 50%) at 1 year (mean survival time, 399 days versus 517 days in controls) and caused an increased incidence of alveolar cell hyperplasia (14/30) compared with controls (5/30). [The Working Group noted the low dose used, the short exposure duration, the small number of animals and the high mortality in the first year.] However, histopathological examination (larynx, trachea, lungs, liver, spleen, gastric tract, kidneys, bladder, and other tissues not further specified) of 30 hamsters that had died or been killed

gave no indication of an increased incidence of neoplasms (Ohyama *et al*., 1988). [The Working Group noted the inadequate reporting of the study and also judged the study design inadequate for carcinogenic effect determination.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Deposition, retention, clearance and metabolism

4.1.1 *Humans*

Data on excretion of gallium have been collected from cancer patients who had received radioactive gallium for radiotherapy or scintigraphy. There was a wide variation in urinary excretion but most subjects excreted about half of the given dose during the 4 days following administration and the major part during the first 8 h. Brucer *et al.* (1953) reported autopsy data from patients who had received intravenous radioactive gallium (^{72}Ga) which showed accumulation in the lung.

Studies by Krakoff *et al.* (1979) showed that an intravenous injection of gallium nitrate at a concentration of 10 mg/mL to patients with advanced cancer was followed by biphasic clearance with half-lives of 87 min and 24.5 h, respectively. Imaging studies using ^{67}Ga have shown that this element localizes in several major tumour categories (Edwards & Hayes, 1969, 1970; Edwards *et al.*, 1970; Winchell *et al.*, 1970; Ha *et al.*, 2000; Nishiyama *et al.*, 2002).

Following exposure, gallium is known to be transported in blood bound to transferrin and to be capable of up-regulating the transferrin receptor (Chitambar & Zivkovic, 1987; Drobyski *et al*., 1996; Jiang *et al*., 2002). The gallium–transferrin complex hence appears to be the primary mechanism by which the gallium ion is presented to the target cellular system.

4.1.2 *Experimental systems*

(*a*) *In-vitro solubility and dissolution in body fluids*

Although the solubility of gallium arsenide in pure water is very low (see Section 1), its dissolution in body fluids is greatly enhanced by endogenous chelating molecules. When incubated in artificial body fluid (Gamble's solution), gallium arsenide progressively releases both gallium and arsenic. A selective leaching appears to take place, probably by chelating components of the solution, whereby more arsenic than gallium is found in solution. The gallium arsenide particle surface is enriched in arsenic, which migrates from the bulk, and which is ultimately oxidized to arsenic oxide (Pierson *et al.*, 1989). When dissolution of gallium arsenide was tested *in vitro* in phosphate buffer and various acids and bases, the amount of dissolved arsenic was highest in phosphate buffer (Yamauchi *et al.*,

1986). These observations help to explain how arsenic may be released from inhaled gallium arsenide particles.

(*b*) *Respiratory system deposition, retention and clearance of gallium compounds*

(i) *Inhalation studies*

Gallium arsenide

Greenspan *et al*. (1991) studied the clearance of inhaled gallium arsenide in male Fischer 344 rats exposed to 0.1, 1.0, 10, 37 and 75 mg/m^3 gallium arsenide (MMAD, 1.2 μm) for 6 h per day on 5 days per week for 13 weeks. The half-life of clearance from the lung was found to be 17 days for both arsenic and gallium. The findings differ from those obtained using intratracheal instillation which often results in preferential clearance of arsenic over gallium (see below).

The National Toxicology Program (2000) reported results from studies in groups of 10 male and 10 female Fischer 344/N rats exposed to particulate aerosols of gallium arsenide (MMAD, 0.81–1.60 μm) by inhalation of concentrations of 0, 0.1, 1, 10, 37 or 75 mg/m^3 for 6 h per day on 5 days per week for 14 weeks. Tissue burden was evaluated at days 23, 45 and 93. Lung weights increased with increasing exposure concentration in males exposed to 1 mg/m^3 or more when examined on days 23 and 45 and in all exposed groups at week 14. In addition, lung weights of exposed rats continued to increase to a greater extent throughout the study compared with those of chamber controls. The percentages of gallium and arsenic in the lung relative to the total lung burden of gallium arsenide were similar at all exposure concentrations throughout the study. The deposition and clearance rates in the lung for gallium and arsenic were similar within each exposure group. Lung clearance half-lives decreased for gallium, from 56 days in rats exposed to 1 mg/m^3 to 20 days in the highest exposure group (75 mg/m^3). Corresponding values for arsenic were 31 and 19 days.

A 2-year study was subsequently performed in rats exposed to 0.01, 0.1 or 1.0 mg/m^3 gallium arsenide using the same experimental conditions as above. Lung weights measured at months 1, 2, 4, 6, 12 and 18 were increased to a greater extent in all male rats exposed to 0.1 or 1.0 mg/m^3 throughout the study than did lung weights of chamber controls and of the group exposed to 0.01 mg/m^3. The percentages of gallium and arsenic in the lung relative to the total lung burden were similar at all exposure concentrations throughout the study because the deposition and clearance rates in the lung for gallium and arsenic were similar within each exposed group. Deposition rates for gallium and arsenic increased with increasing exposure concentration. Lung clearance half-lives of gallium in the group exposed to 1.0 mg/m^3 were considerably less (37 days) than those for the groups exposed to 0.1 (96 days) or 0.01 mg/m^3 (133 days). Lung clearance half-lives of arsenic were similar to those of gallium. The gallium lung tissue burdens at 18 months were 1.60, 13.86 and 22.87 μg/g for groups exposed to 0.01, 0.1 and 1.0 mg/m^3, respectively. Gallium concentrations in whole blood, serum and testes and arsenic concentrations in serum and

testes were above the limits of detection only at the higher exposure concentrations and at the later time points in the study. The mean gallium concentration in whole blood was 0.05 μg/g at 18 months in the highest exposure group; corresponding values were 0.08 μg/g in serum and 1.5 μg/g in testes (National Toxicology Program, 2000).

Gallium oxide

Wolff *et al*. (1984) studied the deposition and retention of single doses of inhaled aggregate radiolabelled gallium oxide ($^{67}Ga_2O_3$) test particles (MMAD, 0.1 μm) in beagle dogs, Fischer 344 rats and CD-1 mice using a 30-min nose-only exposure. In dogs, total gallium deposition was 39 ± 19% (mean ± SD) of the administered dose, pulmonary deposition was 25%, bronchial deposition was 7% and nasopharyngeal deposition was 7%. Corresponding values in rats were 11, 5 and 9% for pulmonary, bronchial and nasopharyngeal deposition, respectively. Pulmonary deposition in mice was estimated to be 15–20% of the administered dose. Whole-body retention was measured and in dogs the long-term plateau represented more than 70% of the particles, compared with 38% and 28% for rats and mice, respectively. The half-life of the long-term component of clearance was 75 ± 19 days for mice, 65 ± 17 days for rats and 52 ± 25 days for dogs.

Wolff *et al.* (1989) presented results of modelling accumulation of particles in rat lung during chronic nose-only inhalation exposure of Fischer 344 rats to 23 mg/m^3 gallium oxide for 2 h per day on 5 days a week for 4 weeks. Impaired clearance occurred early after accumulation of a low burden of the particles. A half-life in the order of 170 days was observed rather than the 65-day half-life reported earlier (Wolff *et al.*, 1984; see above). This impairment of clearance might influence toxicity and the local dose of particles of low solubility in experimental studies.

Battelle Pacific Northwest Laboratories (1990a) carried out 13-week inhalation studies of gallium(III) oxide in male Fischer 344 rats exposed to 0, 0.12, 0.48, 4.8, 24 or 48 mg/m^3 gallium oxide particles (MMAD, ~0.9 μm). Gallium exposure concentrations were approximately equimolar to those used in the studies of gallium arsenide cited above (Greenspan *et al.*, 1991; National Toxicology Program, 2000). As observed with gallium arsenide, following inhalation of gallium oxide, blood and urinary concentrations of gallium were found to be extremely low and only detectable in animals exposed to 24 and 48 mg/m^3 throughout the study. The results indicated that gallium oxide, like gallium arsenide, is not readily absorbed and that, when absorbed, it is rapidly cleared from the blood and either excreted or sequestered in the tissues. Considerable concentrations of gallium were detected in the faeces. Lung burdens increased with increasing exposure concentration. However, when normalized to exposure concentration, accumulation in the lung during the study increased as exposure concentrations increased. Overload may have occurred at gallium oxide concentrations of 24 mg/m^3 and above; this would be in line with the results of Wolff *et al.* (1989).

(ii) *Instillation studies with gallium arsenide*

Webb *et al.* (1984) investigated absorption, excretion and pulmonary retention of gallium arsenide after intratracheal instillation doses of 10, 30 and 100 mg/kg bw (mean volume particle diameter, 12.7 μm) in male Fischer 344 rats. At day 14, gallium was not detected in the blood and urine at any dosage but was retained in the lungs; arsenic retention (measured by F-AAS) ranged from 17 to 32% of the doses given while gallium retention (measured also by F-AAS) ranged from 23 to 42%. In a later study, Webb *et al*. (1986) exposed male Fischer 344 rats to gallium arsenide (100 mg/kg bw) and gallium trioxide (65 mg/kg bw) (equimolar for gallium) by intratracheal instillation (mean volume particle diameters, 12.7 μm and 16.4 μm, respectively). The mean retention of gallium in the lung at day 14 was fairly similar for the two compounds (44% and 36% for gallium arsenide and gallium trioxide, respectively). Webb *et al*. (1987) showed that smaller gallium arsenide particles (mean volume particle diameter, 5.82 μm) had an increased in-vivo dissolution rate and there was increased severity of pulmonary lesions in male Fischer 344 rats after intratracheal instillation of a suspension containing 100 mg/kg bw. Clearance from lung was faster for arsenic (half-life, 4.8 days) than for gallium (half-life, 13.2 days).

Rosner and Carter (1987) studied metabolism and excretion after intratracheal instillation of 5 mg/kg bw gallium arsenide (mean volume particle diameter, 5.8 μm) in Syrian golden hamsters. Blood arsenic concentrations increased from 0.185 ± 0.041 ppm (2.4 μM) after day 1 to 0.279 ± 0.021 ppm (3.7 μM) on day 2. Blood concentrations of arsenic peaked at day 2 after dosing, indicating continued absorption. Of the arsenic, 5% was excreted in the urine during the first 4 days after gallium arsenide instillation compared with 48% after exposure to soluble arsenic compounds. Arsenic derived from gallium arsenide was converted into arsenate (As^{III}), arsenite (As^{V}) and a major metabolite dimethyl arsinic acid, and rapidly excreted. Twenty-seven per cent of the arsenic derived from gallium arsenide were excreted in the faeces the first day after the instillation; this was probably due to lung clearance into gastrointestinal tract after expectoration.

Omura *et al*. (1996a) exposed hamsters to 7.7 mg/kg bw gallium arsenide, 7.7 mg/kg bw indium arsenide or 1.3 mg/kg bw arsenic trioxide by intratracheal instillation twice a week, 14–16 times. Arsenic concentrations in serum on the day after the last instillation were 0.64 μM after gallium arsenide, 0.34 μM after indium arsenide and 1.31 μM after arsenic trioxide. Serum concentrations of gallium and indium were about 20 μM. The results indicated a high retention of both gallium and indium compared with that of arsenic which might be of importance in toxicity from long-term exposure.

Gallium arsenide might in itself impair lung clearance. Aizawa *et al*. (1993) used magnetometric evaluation to study the effects of gallium arsenide on clearance of iron oxide test particles in rabbits. Instillation of 30 mg or 300 mg gallium arsenide per animal in 2 mL saline significantly impaired clearance at 14, 21 and 28 days after exposure. However, although the effect was clear, the dose was high. Impaired clearance might be caused by gallium arsenide itself or by dissolved arsenic-induced inflammation.

(*c*) *Gastrointestinal exposure to gallium*

(i) *Oral and intraperitoneal studies*

Yamauchi *et al*. (1986) studied metabolism and excretion of gallium arsenide (mean volume particle diameter, 14 μm) in Syrian golden hamsters exposed to single doses of 10, 100 or 1000 mg/kg bw in phosphate buffer administered orally through a stomach tube and 100 mg/kg bw intraperitoneally. Urinary excretion of arsenic during the following 120 h was 0.15, 0.11 and 0.05% of the high, medium and low oral doses, respectively, and 0.29% of the intraperitoneal dose. During the same time period, faecal excretion of arsenic was around 80% of the oral doses and 0.38% of the intraperitoneal dose.

Flora *et al*. (1997) exposed groups of male albino rats to single oral doses of 500, 1000 or 2000 mg/kg bw gallium arsenide. Blood was collected at 24 h, and on days 7 and 15 following exposure. Urinary samples were taken at 24 h. Animals were killed on days 1, 7 and 15 and heart tissue was collected. Blood and heart tissue concentrations of gallium and arsenic were determined using GF-AAS and were found to peak at day 7. In a later study, Flora *et al.* (1998) exposed male Wistar albino rats to single doses of 100, 200 or 500 mg/kg bw gallium arsenide or vehicle (control) by gastric intubation. Concentrations of gallium and arsenic were measured at 24 h, and on days 7 and 21 following administration and peaked at day 7 in the blood, liver and kidney but continued to increase up to day 21 in the spleen.

(ii) *Intravenous injection of gallium-67: tracer studies*

Sasaki *et al.* (1982) studied differences in the liver retention of ^{67}Ga (as gallium citrate) administered intravenously in controls and rats fed with the liver carcinogen 3′-methyl-4-dimethylaminobenzene for 20 weeks. They observed that the accumulation of ^{67}Ga in the carcinogen-fed animals at 20 weeks was about 2.3 times greater (per gram of liver) than in the controls. This increase correlated with increases in γ-glutamyl transpeptidase and glucose-6-phosphatase activities at late stages during hepatocarcinogenesis. The most marked change in ^{67}Ga accumulation occurred in the nuclear/whole cell (800 × g) liver fraction suggesting that ^{67}Ga may bind to components in this fraction, induced by 3′-methyl-4-dimethylaminobenzene.

4.1.3 *Data relevant to an evaluation of gallium arsenide as an arsenic compound*

(*a*) *Metabolism of the arsenic oxides*

Radabaugh and coworkers (2002) recently characterized arsenate reductase enzyme and identified it as a purine nucleoside phosphorylase, an ubiquitous enzyme that required dihydrolipoic acid for maximum reduction of arsenate As^{V} to arsenite As^{III} in mammals. [The valences of different forms of arsenic and their metabolites are indicated by superscript roman numerals such as it is reported in scientific publications.] The As^{III} formed may then be methylated to MMA^{V} and to DMA^{V} by methyl transferases which have been partially characterized (Zakharyan *et al.*, 1995; Wildfang *et al.*, 1998; Styblo *et al.*, 1999).

In mice, the highest methylating activity occurred in testes followed by kidney, liver and lung (Healy *et al.*, 1998). The analogous enzymatic reduction of MMA^{V} to monomethylarsonous acid (MMA^{III}) was also demonstrated in hamster; MMA^{V} reductase-specific activities have been shown in all organs (Sampayo-Reyes *et al.*, 2000).

(*b*) *Variation in arsenic methylation between species*

Most human organs can metabolize arsenic by oxidation/reduction reactions, methylation and protein binding. However, there is a pronounced species difference in this metabolism. Arsenic is strongly retained in rat erythrocytes but not in those of other species. The unique disposition of arsenic in rats may be due to the pronounced biliary excretion of MMA^{III} and erythrocyte of DMA^{III} (Gregus *et al.*, 2000; Shiobara *et al.*, 2001) which may explain the lower toxicity of arsenic in rats. Thus, previous scientific committees have stated that they did not recommend rats for arsenic oxide disposition studies (National Academy of Sciences, 1977; Aposhian, 1997). Most experimental animals excrete very little MMA [valence not specified] in urine compared to humans (Vahter, 1999) and some animal species, in particular guinea-pigs and several non-human primates, are unable to methylate arsenic at all (Healy *et al.*, 1997; Vahter, 1999; Wildfang *et al.*, 2001). The effect of the inability to methylate As^{III} compounds on toxicity following repeated dosing is unknown but methylation has long been considered the primary mechanism of detoxification of arsenic in mammals (Buchet *et al.*, 1981). However, non-methylator animals were not found to be more sensitive to the acute effect of arsenic than methylators in the few tests that have been performed. The toxic response of non-methylators needs to be examined in more detail. At present, the most toxic arsenic species is thought to be the MMA^{III} (Petrick *et al.*, 2000; Styblo *et al.*, 2000; Petrick *et al.*, 2001), leading to the view that this methylation should be considered as bioactivation of the metalloid rather than detoxification.

Arsenic detoxification mechanisms other than methylation have been poorly investigated. The fact that man is more than 10 times more sensitive to the effect of arsenic oxides when compared to all other animal species is remarkable. The explanation of this difference in sensitivity is important in order to understand the mechanism of action of arsenic (see IARC, 2004).

4.2 Toxic effects

4.2.1 *Humans*

There are no published reports specific to the toxicity of gallium arsenide in humans.

4.2.2 *Experimental systems*

(*a*) *Gallium arsenide and gallium oxide*

(i) *Non-neoplastic and pre-neoplastic effects in the respiratory tract*

Results of studies undertaken by the National Toxicology Program (2000) (see also Section 3.1) confirmed that the respiratory tract was the primary site of toxicity, indicated by a spectrum of inflammatory and proliferative lesions of the lung. As described in Sections 3.1.1 and 3.1.2, and in Table 2, groups of 50 male and 50 female $B6C3F_1$ mice and groups of 50 male and 50 female Fischer 344/N rats, 6 weeks of age, were exposed by inhalation to gallium arsenide particulate (purity, > 98%; MMAD, 0.8–1.0 μm; GSD, 1.8–1.9 μm) at concentrations of 0, 0.1, 0.5 or 1 mg/m^3 for mice and 0, 0.01, 0.1 and 1 mg/m^3 for rats, for 6 h per day on 5 days per week for 105 or 106 weeks. In mice, non-neoplastic effects were observed in the lung (which included focal suppurative inflammation, focal chronic inflammation, histiocyte infiltration, hyperplasia of the alveolar epithelium, proteinosis of the alveoli and tracheobronchial lymph nodes). The non-neoplastic effects observed in the lung of exposed rats included atypical hyperplasia, active chronic inflammation, proteinosis and metaplasia of the alveolar epithelium in both sexes. In male rats, hyperplasia of the alveolar epithelium of the lung and chronic active inflammation, squamous metaplasia and hyperplasia of the epiglottis and the larynx were observed (National Toxicology Program, 2000).

The most prominent toxic effect of gallium arsenide after a single intratracheal instillation to rats is pulmonary inflammation (Webb *et al*., 1987; Goering *et al.*, 1988). Histopathological changes and changes in tissue concentrations of protein, lipid, and DNA have been observed (Webb *et al.*, 1986). The effects caused by gallium arsenide (100 mg/kg bw) were compared with those elicited by equimolar gallium oxide (65 mg/kg bw) and maximally-tolerated amounts of (17 mg/kg bw, 0.25 equimolar) arsenious (III) acid (Webb *et al.*, 1986). Two weeks after exposure to gallium arsenide, increases in lipid concentrations, comparable to those observed following exposure to equimolar gallium, and increases in protein concentrations similar to those found after exposure to arsenious acid were observed. DNA concentrations were significantly increased after exposure to gallium arsenide but not to the same magnitude as those seen after arsenious acid exposure (arsenious acid was given at 0.25 times the molar dose of gallium arsenide). Only exposure to arsenious acid resulted in increases in 4-hydroxyproline, an indicator of a fibrotic process. Lung wet weights, lung wet weight/body weight and lung dry weights were all increased after instillation of gallium arsenide but not after instillation of gallium oxide or arsenious acid. Goering *et al.* (1988) reported similar histopathological changes in the lungs of rats treated with gallium arsenide in the same conditions.

In a 16-day inhalation study (National Toxicology Program, 2000) of rats exposed to gallium arsenide at concentrations of 0, 1, 10, 37, 75 or 150 mg/m^3, statistically-significant increases in the weights of lungs and liver relative to body weight were noted in animals exposed to concentrations of 1 mg/m^3 and greater. These effects were noted only for lungs

following exposure to 0.1 mg/m^3 and above in a 14-week study. When the studies were repeated in mice, only the lungs were found to show increases relative to body weights.

(ii) *Haematological effects*

A study (National Toxicology Program, 2000; see Section 4.1.2) of mice and rats exposed to gallium arsenide at chamber concentrations of 0, 0.1, 1, 10, 37 or 75 mg/m^3 for 14 weeks, showed statistically-significant decreases in haematocrit and haemoglobin concentrations, and increased numbers of erythrocytes and reticulocytes at 14 weeks in both species exposed to 37 and 75 mg/m^3. Statistically-significant decreases in leucocyte numbers were noted in rats exposed to the two highest doses, whereas increases in leucocyte numbers were observed in mice exposed to the three highest doses. Zinc protoporphyrin/haeme ratios increased in male and female mice exposed to the two highest doses while methaemoglobin increased only in female rats.

Effects on the haem biosynthetic pathway

In the 14-week exposure study cited above (National Toxicology Program, 2000), concentrations of δ-aminolevulinic acid (ALA) and porphobilinogen were not increased in urine of rats exposed by inhalation to gallium arsenide, suggesting that the effect of the porphyria, as it relates to haeme synthesis, was marginal.

Goering and colleagues (1988) observed systemic effects after intratracheal administration of 50, 100 and 200 mg/kg bw gallium arsenide to rats. Activity of δ-aminolevulinic acid dehydratase (ALAD) in blood and urinary excretion of δ-aminolevulinic acid (ALA) were examined. A dose-dependent inhibition of ALAD activity in blood and an increase in excretion of ALA in urine were observed with a maximum response 3–6 days after exposure. A urinary porphyrin excretion pattern characteristic of arsenic exposure (Woods & Fowler, 1978) was also observed in these animals (Bakewell *et al.*, 1988).

In-vitro studies with gallium nitrate, sodium arsenite and sodium arsenate showed that 75 μM gallium nitrate inhibited the activity of blood ALAD and 2 μM gallium nitrate inhibited liver and kidney ALAD. The inorganic arsenic compounds inhibited ALAD in blood at much higher concentrations (15 mM, 200-fold) (Goering *et al.*, 1988). Subsequent in-vivo and in-vitro studies on ALAD in blood, liver and kidney showed that the mechanism of gallium inhibition involves zinc displacement from the sulfhydryl group of the enzyme active site (Goering & Rehm, 1990).

(iii) *Immunological effects*

A variety of changes have been reported in animals exposed to gallium arsenide including inhibition of T-cell proliferation and suppression of immunological functions at locations distal to a single exposure site (Sikorski *et al*., 1989; Burns *et al.*, 1991; Burns & Munson, 1993; Hartmann & McCoy, 1996). The effects included decreases in both humoral and cellular antibody response. The dissolution of gallium arsenide to form gallium and arsenic oxides may be the origin of the effects; arsenic has been shown to be the primary

immunosuppressive component of gallium arsenide (Burns *et al.*, 1991), but it was unclear whether all the immunological effects reported were caused by dissolved arsenic.

(*b*) *Other gallium compounds*

(i) In vitro

Studies by Chitambar and Seligman (1986), Chitambar and co-workers (1988, 1990, 1991) and Narasimhan *et al.* (1992) have shown that transferrin-gallium exerts its toxic effects at the molecular level by inhibiting ribonucleotide reductase, specifically by displacing iron from the M2 subunit of this enzyme.

(ii) In vivo

Early studies by Dudley and Levine (1949) demonstrated the acute renal toxicity of gallium lactate 3 or 4 days after its intravenous injection in rats. Studies by Hart *et al.* (1971) and Adamson *et al.* (1975) further extended the database on the renal toxicity of gallium nitrate; a limiting factor in its use in the treatment of tumours.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

There have been several studies that have reported that workers in the semiconductor industry experience increased rates of spontaneous abortion, but the evidence is inconclusive (Elliot *et al.*, 1999). No single metal has been denoted as a more possible causative agent than any other because of the complex chemical exposures, and other factors, encountered in these environments (Fowler & Sexton, 2002).

4.3.2 *Animals*

(*a*) *Testicular function changes*

(i) *Gallium arsenide*

Testicular toxicity has been reported in rats and hamsters after intratracheal administration of 7.7 mg/kg bw gallium arsenide twice a week for a total of 8 weeks (Omura *et al.*, 1996a,b). A significant decrease in sperm count and in the proportion of morphologically-abnormal sperm were found in the epididymis in the gallium arsenide-treated rats. In hamsters, gallium arsenide caused testicular spermatid retention and epididymal sperm reduction. Animals treated with arsenic trioxide (1.3 mg/kg) or indium arsenide (7.7 mg/kg bw) did not show any testicular toxicities. The arsenic concentrations in serum of gallium arsenide-treated rats were almost twice those found in arsenic trioxide-treated rats. In addition, the molar concentration of gallium was found to be 10–20-fold higher than that of arsenic in gallium arsenide-treated rats (Omura *et al.*, 1996a). In contrast, the arsenic concentrations in serum of gallium arsenide-treated hamsters were less than half of those

found in arsenic trioxide-treated hamsters. Moreover, the molar concentration of gallium was 32 times higher than that of arsenic in gallium arsenide-treated hamsters. Therefore gallium may play a main role in the testicular toxicity in hamsters (Omura *et al.*, 1996b).

Similar testicular toxicities were observed in 14-week and 2-year gallium arsenide inhalation studies (National Toxicology Program, 2000). The effects included decreases in epididymal weights and sperm motility in both rats and mice exposed to 37 and 75 mg/m^3 in the 14-week study. Decreases in epididymal weights and an epididymal hypospermia were also observed in mice exposed to 10 mg/m^3. Decreased testicular weights, genital atrophy and interstitial hyperplasia were observed in rats exposed to 1 mg/m^3 of gallium arsenide in the 2-year study.

(ii) *Gallium oxide*

In a 13-week study of gallium oxide in male rats and mice, exposure to concentrations of 0, 0.16, 0.64, 6.4, 32 or 64 mg/m^3 were found to have no effect on male rat reproductive parameters. However, exposure to gallium oxide at 32 mg/m^3 or greater caused decreases in cauda epididymis and testis weights. Decreases in epididymal sperm motility and concentration were observed in animals exposed to 64 mg/m^3. Testicular degeneration and increased cellular debris in the epididymis were observed in mice exposed to gallium oxide at 64 mg/m^3 (Battelle Pacific Northwest Laboratories, 1990a,b).

(*b*) *Effects on estrous cycles, gestation and foetal development*

In a 13-week study of gallium oxide in female rats and mice, there was no effect of exposure to concentrations of 0.16–64 mg/m^3 on the estrous cycles of either animal species (Battelle Pacific Northwest Laboratories, 1990a,b).

Studies to assess the developmental toxicity of gallium arsenide were performed with Sprague-Dawley rats and Swiss mice exposed to 0, 10, 37 or 75 mg/m^3 gallium arsenide by inhalation 6 h per day, 7 days per week. Rats were exposed on gestation days 4 through 19. There were no signs of maternal toxicity. Minimal effects on the fetuses were noted, including a marginal reduction in body weight in the group exposed to 75 mg/m^3 and concentration-dependent reduced ossification of the sternebrae. There was a non-significant increase in the incidence of incompletely ossified vertebral centra. Mice were exposed on gestation days 4 through 17. Considerable fetal and maternal toxicity was seen in groups exposed to 37 and 75 mg/m^3 gallium arsenide, with 50% of the female animals found dead or moribund. Most exposed females were hypoactive, had laboured breathing and failed to gain weight. The number of resorptions per litter was significantly increased and occurred earlier, while the number of corpora lutea per dam and the number of live fetuses per litter were significantly decreased. Fetal weights were reduced in all exposed groups. Although not statistically significant, various skeletal malformations were observed including cleft palate, encephalocele, and vertebral defects (Battelle Pacific Northwest Laboratories, 1990c; Mast *et al.*, 1991).

4.4 Genetic and related effects (see Table 3)

Gallium arsenide (10 000 μg/plate) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, TA102 or TA1535, with or without induced rat or hamster liver S9 enzymes (Zeiger *et al.*, 1992). No increase in the frequency of micronucleated normochromatic erythrocytes was seen in peripheral blood samples from male or female $B6C3F_1$ mice exposed to gallium arsenide by inhalation in concentrations up to 75 mg/m^3, during a 14-week study (National Toxicology Program, 2000). The majority of these experiments were carried out assuming arsenite (As^{III}) was the toxic species; however, there is evidence that it is not. It appears that dimethyl arsinous acid may be a carcinogen but that the most toxic arsenic species may be MMA^{III} (see Section 4.1.3). It is believed that many studies have assigned a toxic dose to arsenate but the effect was actually the result of the reduction of arsenate (As^{V}) to arsenite (As^{III}) (Carter *et al.*, 1999, 2003). It is also of concern that experiments with arsenate using cells have been done without consideration of the concentration of phosphate, an arsenate uptake inhibitor (Huang & Lee, 1996).

4.5 Mechanistic considerations

The hypothesis used to interpret the carcinogenesis results appears to accept the finding that gallium arsenide causes cancer in female rats and that the non-neoplastic hyperplasia is a precursor to neoplasms. The lung effects appear to be 'point of contact' effects. The mechanism of lung cancer fits with a highly toxic compound which kills many different cells without killing the host organism. This leads to regenerative cell proliferation that magnifies any errors in DNA replication and results in enough errors to make organ neoplastic changes in the lung. Some systemic effects were found to be sex-specific and, therefore, a selectivity of response between males and females is not surprising.

It is clear that there is partial dissolution of gallium arsenide particles *in vivo* and that while the majority of a dose of gallium arsenide remains in the lung, there is redistribution of solubilized gallium and arsenic to other organ systems. This results in a variety of toxic effects including inhibition of haeme biosynthesis in a number of organ systems, testicular damage and impaired immune function. Some of the biochemical effects, such as inhibition of haeme pathway enzymes such as ALAD, appear to be relatively specific. However, more pronounced cellular changes in target organ systems such as the kidney, testes, or immune system may be the result of gallium or arsenic or combined exposure to these elements. Further mechanistic research is needed to elucidate the primary underlying roles played by these elements in organ systems outside the lungs.

There is evidence from in-vitro test systems that ionic gallium, such as the gallium transferrin complex, may influence the carcinogenic process by inducing apoptosis at low doses and producing necrosis at high doses in cancer cell lines (Jiang *et al.*, 2002).

Table 3. Genetic and related effects of gallium arsenide

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA97, TA98, TA100, TA108, TA1535, reverse mutation	–	–	10 000 µg/plate	Zeiger *et al.* (1992)
Formation of micronuclei in binucleates, cytochalasin-B assay, Syrian hamster embryo cells *in vitro*	–		10 µg/mL	Gibson *et al.* (1997)
Formation of micronuclei, B6C3F$_1$ mice erythrocytes in peripheral blood *in vivo*	–		75 µg/m^3 inhalation (14 wk)	National Toxicology Program (2000)
Cell transformation, Syrian hamster embryo cells *in vitro*	+		0.5 µg/mL	Kerckaert *et al.* (1996)

[a] +, positive; –, negative
[b] LED, lowest effective dose; HID, highest ineffective dose

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Gallium arsenide is extensively used in the microelectronics industry because of its photovoltaic properties. Gallium arsenide is produced as high purity single crystals and cut into wafers and other shapes which are used primarily for integrated circuits and opto-electronic devices. Exposure to gallium arsenide occurs predominantly in the micro-electronics industry where workers are involved in the production of gallium arsenide crystals, ingots and wafers, grinding and sawing operations, device fabrication and sand-blasting and clean-up activities.

5.2 Human carcinogenicity data

See Introduction to the Monographs on Gallium Arsenide and Indium Phosphide.

5.3 Animal carcinogenicity data

Gallium arsenide was tested for carcinogenicity in a single study by chronic inhalation exposure in mice and rats. In female rats exposed to the highest concentration, significantly increased incidences of alveolar/bronchiolar neoplasms, benign pheochromocytoma of the adrenal medulla and mononuclear-cell leukaemia were observed. There was no evidence of carcinogenic activity in male rats, or in male or female mice.

Gallium arsenide was tested by intratracheal instillation in male hamsters and showed no carcinogenic response. However, due to inadequacies in design and reporting, the study did not contribute to this evaluation.

5.4 Other relevant data

Gallium arsenide has low solubility. There is in-vitro and in-vivo evidence that gallium arsenide releases gallium and arsenic moieties.

Uptake from the gastrointestinal tract is low. In inhalation studies, lung retention of inhaled gallium arsenide has been shown to be influenced by toxic effects from gallium arsenide itself. Tissue burdens are highest in the lung. Concentrations of gallium and arsenic in blood and serum remain low in long-term inhalation studies. Concentrations of gallium in testes show evidence of accumulation, but at a much lower level than in the lung. After intratracheal instillation of gallium arsenide, data indicate slower elimination and higher serum concentrations of gallium compared with arsenic.

The most prominent toxic effect of gallium arsenide is pulmonary inflammation, which may occur after a single intratracheal dose. Gallium arsenide and gallium nitrate inhibit the activity of δ-aminolevulinic acid dehydratase.

Immunological effects of exposure to gallium arsenide include inhibition of T-cell proliferation and decrease of both humoral and cellular immune response. These effects are partly due to the arsenic moiety.

Testicular toxicity was observed in rats and hamsters exposed to gallium arsenide by intratracheal administration, while animals treated with arsenic trioxide and indium arsenide did not show these effects. In inhalation studies with gallium arsenide, decreased epididymal weights and reduced sperm mobility were observed. A number of reproductive toxic effects were reported following exposure of pregnant rodents to gallium arsenide. These effects were more severe in mice than in rats.

Based on limited data, gallium arsenide does not show genotoxic activity.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of gallium arsenide.

There is *limited evidence* in experimental animals for the carcinogenicity of gallium arsenide.

Overall evaluation

Gallium arsenide is *carcinogenic to humans (Group 1)*.

The Working Group noted that there were no data on cancer in humans and that gallium arsenide is, at best, a weak carcinogen in experimental animals. In reaching an overall evaluation of *Group 1*, the Working Group noted the potential for gallium arsenide to cause cancer through two separate mechanisms of action. Once in the body, gallium arsenide releases a small amount of its arsenic, which behaves as inorganic arsenic at the sites where it is distributed. (Arsenic and arsenic compounds have been evaluated as IARC Group 1, carcinogenic to humans.) At the same time, the gallium moiety may be responsible for the lung cancers observed in the study in female rats, due to the apparent resistance of rats to the carcinogenic potential of arsenic that is manifest in humans. The similarity of toxicochemical responses observed in subchronic studies with gallium arsenide and gallium oxide adds weight to the finding that the gallium moiety is active and suggests that a carcinogenic response might be observed with other gallium compounds. The observed findings may also be a result of the combination of the two moieties.

6. References

ACGIH Worldwide® (2003) *Documentation of the TLVs® and BEIs® with Other Worldwide Occupational Exposure Values — CD-ROM — 2003*, Cincinnati, OH

Adamson, R.H., Canellos, G.P. & Sieber, S.M. (1975) Studies on the antitumor activity of gallium nitrate (NSC-15200) and other group IIIa metal salts. *Cancer Chemother. Rep.*, **59**, 599–610

Afonso, A.M., Santana, J.J. & García Montelongo, F.J. (1985) Pyrocatechol-1-aldehyde 2-benzothiazolylhydrazone as reagent for the spectrofluorimetric determination of nanogram amounts of gallium in urine and blood serum. *Anal. Lett*., **A18**, 1003–1012

Aizawa, Y., Takata, T., Karube, H., Tatsumi, H., Inokuchi, N., Kotani, M. & Chiyotani, K. (1993) Magnetometric evaluation of the effects of gallium arsenide on the clearance and relaxation of iron particles. *Ind. Health*, **31**, 143–153

Anthemidis, A.N., Zachariadis, G.A. & Stratis, J.A. (2003) Gallium trace on-line preconcentration/separation and determination using a polyurethane foam mini-column and flame atomic absorption spectrometry. Application in aluminum alloys, natural waters and urine. *Talanta*, **60**, 929–936

Aposhian, H.V. (1997) Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. *Annu. Rev. Pharmacol. Toxicol.*, **37**, 397–419

Apostoli, P., Bartoli, D., Alessio, L. & Buchet, J.P. (1999) Biological monitoring of occupational exposure to inorganic arsenic. *Occup. environ. Med.*, **56**, 825–832

Bakewell, W.E., Goering, P.L., Moorman, M.P. & Fowler, B.A. (1988) Arsine (AsH_3) and gallium arsenide (GAAS)-induced alterations in heme metabolism (Abstract). *Toxicologist*, **8**, 20

Battelle Pacific Northwest Laboratories (1990a) *Thirteen-week Subchronic Inhalation Toxicity Study Report of Gallium Oxide in Rats*, Final report (NIH No. N01-ES-85211)

Battelle Pacific Northwest Laboratories (1990b) *Thirteen-week Subchronic Inhalation Toxicity Study Report of Gallium Oxide in Mice*, Final report (NIH No. N01-ES-85211)

Battelle Pacific Northwest Laboratories (1990c) *Inhalation Developmental Toxicology Studies: Gallium Arsenide in Mice and Rats*, Final report (NIH No. N01-ES-70153)

Beliles, R.P. (1994) The metals. In: Clayton, G.D. & Clayton, F.E., eds, *Patty's Industrial Hygiene and Toxicology*, 4th Ed., Vol. 2C, John Wiley & Sons, New York, pp. 1879–2013

Beltrán Lucena, R., Morales, E. & Gomez-Ariza, J.L. (1994) Spectrophotometric determination of gallium in biological materials at nanogram levels with thiocarbohydrazone derivatives. *Farmaco*, **49**, 291–295

Brucer, M., Andrews, G.A. & Bruner, H.D. (1953) A study of gallium. *Radiology*, **61**, 534–613

Buchet, J.P., Lauwerys, R. & Roels, H. (1981) Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate, or dimethylarsinate in man. *Int. arch. occup. environ. Health*, **48**, 71–79

Burguera, M. & Burguera, J.L. (1997) Analytical methodology for speciation of arsenic in environmental and biological samples. *Talanta*, **44**, 1581–1604

Burns, L.A. & Munson, A.E. (1993) Gallium arsenide selectively inhibits T cell proliferation and alters expression of CD25 (IL-2R/p55). *J. Pharmacol. exp. Ther*., **265**, 178–186

Burns, L.A., Sikorski, E.E., Saady, J.J. & Munson, A.E. (1991) Evidence for arsenic as the immunosuppressive component of gallium arsenide. *Toxicol. appl. Pharmacol*., **110**, 157–169

Cano Pavón, J.M., Ureña Pozo, E. & Garcia de Torres, A. (1988) Spectrofluorimetric determination of gallium with salicylaldehyde carbohydrazone and its application to the analysis of biological samples and alloys. *Analyst*, **113**, 443–445

Cano Pavón, J.M., Garcia de Torres, A. & Ureña Pozo, M.E. (1990) Simultaneous determination of gallium and aluminium in biological samples by conventional luminescence and derivative synchronous fluorescence spectrometry. *Talanta*, **37**, 385–391

Carter, D.E., Peraza, M.A., Ayala-Fierro, F., Casarez, E., Barber, D.S. & Winski, S.L. (1999) Arsenic metabolism after pulmonary exposure. In: Chappell, W.R., Abernathy, C.O. & Calderon, R.L., eds, *Arsenic Exposure and Health Effects*, Amsterdam, Elsevier, pp. 299–309

Carter, D.E., Aposhian, H.V. & Gandolfi, A.J. (2003) The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxico-chemical review. *Toxicol. appl. Pharmacol.*, **193**, 309–334

Chakrabarti, N.B. (1992) GaAs integrated circuits. *J. Inst. Electron. Telecommun. Eng.*, **38**, 163–178

Chemical Information Services (2003) *Directory of World Chemical Producers (Version 2003)*, Dallas, TX (http://www.chemicalinfo.com, accessed 18.09.2003)

Chitambar, C.R. & Seligman, P.A. (1986) Effects of different transferrin forms on transferrin receptor expression, iron uptake, and cellular proliferation of human leukemic H160 cells. Mechanisms responsible for the specific cytotoxicity of transferrin-gallium. *J. clin. Invest.*, **78**, 1538–1546

Chitambar, C.R. & Zivkovic, Z. (1987) Uptake of gallium-67 by human leukemic cells: Demonstration of transferrin receptor-dependent and transferrin-independent mechanisms. *Cancer Res.*, **47**, 3939–3934

Chitambar, C.R., Matthaeus, W.G., Antholine, W.E., Graff, K. & O'Brien, W.J. (1988) Inhibition of leukemic HL60 cell growth by transferrin-gallium: Effects on ribonucleotide reductase and demonstration of drug synergy with hydroxyurea. *Blood*, **72**, 1930–1936

Chitambar, C.R., Zivkovic-Gilgenbach, Z., Narasimhan, J. & Antholine, W.E. (1990) Development of drug resistance to gallium nitrate through modulation of cellular iron uptake. *Cancer Res.*, **50**, 4468–4472

Chitambar, C.R., Narasimhan, J., Guy, J., Sem, D.S. & O'Brien, W.J. (1991) Inhibition of ribonucleotide reductase by gallium in murine leukemic L1210 cells. *Cancer Res.*, **51**, 6199–6201

Drobyski, W.R., Ul-Haq, R., Majewski, D. & Chitambar, C.R. (1996) Modulation of in-vitro and in-vivo T-cell responses by transferrin-gallium and gallium nitrate. *Blood*, **88**, 3056–3064

Dudley, H.C. & Levine, M.D. (1949) Studies of the toxic action of gallium. *J. Pharmacol. exp. Ther.*, **95**, 487–493

Edwards, C.L. & Hayes, R.L. (1969) Tumor scanning with ^{67}Ga-citrate. *J. nucl. Med.,* **10**, 103–105

Edwards, C.L. & Hayes, R.L. (1970) Scanning malignant neoplasms with gallium 67. *J. am. med. Assoc.*, **212**, 1182–1190

Edwards, C.L., Nelson, B. & Hayes, R.L. (1970) Localization of gallium in human tumors. *Clin. Res.*, **18**, 89

Flora, S.J.S., Dube, S.N., Vijayaraghavan, R. & Pant, S.C. (1997) Changes in certain hematological and physiological variables following single gallium arsenide exposure in rats. *Biol. Trace Elem. Res.*, **58**, 197–208

Flora, S.J.S., Kumar, P., Kannan, G.M. & Rai, G.P. (1998) Acute oral gallium arsenide exposure and changes in certain hematological, hepatic, renal and immunological indices at different time intervals in male Wistar rats. *Toxicol. Lett.*, **94**, 103–113

Fowler, B.A. & Sexton, M.J. (2002) *Chapter 18. Semiconductors.* In: Bibudhendra Sarkar, ed., *Heavy Metals in the Environment*, New York, Marcel Dekker, Inc., pp. 631–645

Gibson, D.P., Brauninger, R., Shaffi, H.S., Kerckaert, G.A., Leboeuf, R.A., Isfort, R.J. & Aardema, M.J. (1997) Induction of micronuclei in Syrian hamster embryo cells: Comparison to results in the SHE cell transformation assay for National Toxicology Program test chemicals. *Mutat. Res.*, **392**, 61–70

Goering, P.L. & Rehm, S. (1990) Inhibition of liver, kidney, and erythrocyte δ-aminolevulinic acid dehydratase (porphobilinogen synthase) by gallium in the rat. *Environ. Res.*, **53**, 135–151

Goering, P.L., Maronpot, R.R. & Fowler, B.A. (1988) Effect of intratracheal gallium arsenide administration on δ-aminolevulinic acid dehydratase in rats: relationship to urinary excretion of aminolevulinic acid. *Toxicol. appl. Pharmacol.*, **92**, 179–193

Greber, J.F. (2003) Gallium and gallium compounds. In: *Ullmann's Encyclopedia of Industrial Chemistry*, 6th rev. Ed., Vol. 15, Weinheim, Wiley-VCH Verlag GmbH & Co., pp. 235–240

Greenspan, B.J., Dill, J.A., Mast, T.J., Chou, B.J., Stoney, K.H., Morrissey, R. & Roycroft, J. (1991) Lung clearance of inhaled gallium arsenide. *Toxicologist*, **11**, 234

Gregus, Z., Gyurasics, A. & Csanaky, I. (2000) Biliary and urinary excretion of inorganic arsenic: Monomethylarsonous acid as a major biliary metabolite in rats. *Toxicol. Sci.*, **56**, 18–25

Greschonig, H., Schmid, M.G. & Gübitz, G. (1998) Capillary electrophoretic separation of inorganic and organic arsenic compounds. *Fresenius J. anal. Chem.*, **362**, 218–223

Ha, C.S., Choe, J.-G., Kong, J.S., Allen, P.K., Oh, Y.K., Cox, J.D. & Edmund, E.K. (2000) Agreement rates among single photon emission computed tomography using gallium-67, computed axial tomography and lymphangiography for Hodgkin disease and correlation of image findings with clinical outcome. *Cancer*, **89**, 1371–1379

Hakala, E. & Pyy, L. (1995) Assessment of exposure to inorganic arsenic by determining the arsenic species excreted in urine. *Toxicol. Lett.*, **77**, 249–258

Harrison, R.J. (1986) Gallium arsenide. In: LaDou, J., ed., *Occupational Medicine: The Microelectronics Industry*, Vol. 1, Philadelphia, PA, Hanley & Belfus, pp. 49–58

Hart, M.M., Smith, C.F., Yancey, S.T. & Adamson, R.H. (1971) Toxicity and antitumor activity of gallium nitrate and periodically related metal salts. *J. natl Cancer Inst.*, **47**, 1121–1127

Hartmann, C.B. & McCoy, K.L. (1996) Gallium arsenide augments antigen processing by peritoneal macrophages for $CD4^+$ helper T cell stimulation. *Toxicol. appl. Pharmacol.*, **141**, 365–372

Healy, S.M., Zakharyan, R.A. & Aposhian, H.V. (1997) Enzymatic methylation of arsenic compounds: IV. In vitro and in vivo deficiency of the methylation of arsenite and monomethylarsonic acid in the guinea pig. *Mutat. Res.*, **386**, 229–239

Healy, S.M., Casarez, E.A., Ayala-Fierro, F. & Aposhian, H.V. (1998) Enzymatic methylation of arsenic compounds. *Toxicol. appl. Pharmacol.*, **148**, 65–70

Heydorn, K. (1984) *Neutron Activation Analysis for Clinical Trace Element Research*, Vol. II, Boca Raton, FL, CRC Press, p. 72

Huang, R.-N. & Lee, T.-C. (1996) Cellular uptake of trivalent arsenite and pentavalent arsenate in KB cells cultured in phosphate-free medium. *Toxicol. appl. Pharmacol.*, **136**, 243–249

IARC (2004) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 84, *Some Drinking-Water Disinfectants and Contaminants, including Arsenic*, Lyon, IARC*Press*

Ito, M. & Shooter, D. (2002) Detection and determination of volatile metal compounds in the atmosphere by a Mist-UV sampling system. *Atmos. Environ.*, **36**, 1499–1508

Iyengar, V. & Woittiez, J. (1988) Trace elements in human clinical specimens: Evaluation of literature data to identify reference values. *Clin. Chem.*, **34**, 474–481

Iyengar, G.V., Kollmer, W.E. & Bowen, H.J.M. (1978) *The Elemental Composition of Human Tissues and Body fluids, A Compilation of Values for Adults*, Weinheim, Verlag Chemie

Jakubowski, M., Trzcinka-Ochocka, M., Razniewska, G. & Matczak, W. (1998) Biological monitoring of occupational exposure to arsenic by determining urinary content of inorganic arsenic and its methylated metabolites. *Int. Arch. occup. environ. Health*, **71**, S29–S32

Jiang, X.P., Wang, F., Yang, D.C., Elliott, R.L. & Head, J.F. (2002) Induction of apoptosis by iron depletion in the human breast cancer MCF-7 cell line and the 13762NF rat mammary adenocarcinoma *in vivo*. *Anticancer Res.*, **22**, 2685–2692

Kerckaert, G.A., Brauninger, R., LeBoeuf, R.A. & Isfort, R.J. (1996) Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ. Health Perspect.*, **104** (Suppl. 5), 1075–1084

Kitsunai, M. & Yuki, T. (1994) Review: How gallium arsenide wafers are made. *Appl. organometal. Chem*., **8**, 167–174

Krakoff, I.H., Newman, R.A. & Goldberg, R.S. (1979) Clinical toxicologic and pharmacologic studies of gallium nitrate. Cancer, 44, 1722–1727

Kramer, D.A. (1988) *Gallium and Gallium Arsenide: Supply, Technology, and Uses.* Information Circular 9208, Washington DC, US Department of the Interior, Bureau of Mines

Kramer, D.A. (1996–2004) *Mineral Commodity Summary: Gallium*, Reston, VA, US Geological Survey (http://minerals.usgs.gov/minerals/pubs/commodity/gallium/index.html; accessed 20.09.2003)

Kramer, D.A. (2002) *Minerals Yearbook: Gallium*, Reston, VA, US Geological Survey (http://minerals.usgs.gov/minerals/pubs/commodity/gallium/index.html; accessed 20.09.2003)

Kramer, D.A. (2003) *Mineral Commodity Summary: Gallium*, Reston, VA, US Geological Survey (http://minerals.usgs.gov/minerals/pubs/commodity/gallium/index.html; accessed 20.09.2003)

Kucera, J., Havránek, V., Smolík, J., Schwarz, J., Vesely, V., Kugler, J., Sykorová, I. & Šantroch, J. (1999) INAA and PIXE of atmospheric and combustion aerosols. *Biol. trace Elem. Res.*, **71–72**, 233–245

Lide, D.R., ed. (2003) *CRC Handbook of Chemistry and Physics*, 84th Ed., Boca Raton, FL, CRC Press LLC, p. 4-58

Ma, D., Okamoto, Y., Kumamaru, T. & Iwamoto, E. (1999) Determination of gallium by graphite furnace atomic absorption spectrometry with combined use of a tungsten-coated L'vov platform tube and a chemical modification technique. *Anal. Chim. Acta*, **390**, 201–206

Mast, T.J., Dill, J.A., Greenspan, B.J., Evanoff, J.J., Morrissey, R.E. & Schwetz, B.A. (1991) The development toxicity of inhaled gallium arsenide in rodents (Abstract). *Teratology*, **43**, 455–456

Nakamura, K., Fujimori, M., Tsuchiya, H. & Orii, H. (1982) Determination of gallium in biological materials by electrothermal atomic absorption spectrometry. *Anal. Chim. Acta*, **138**, 129–136

Narasimhan, J., Antholine, W.E. & Chitambar, C.R. (1992) Effect of gallium on the tyrosyl radical of the iron-dependent M2 subunit of ribonucleotide reductase. *Biochem. Pharmacol.*, **44**, 2403–2408

National Academy of Sciences (1977) *Medical and Biological Effects of Environmental Pollutants, Arsenic*, Washington, DC, National Research Council

National Institute for Occupational Safety and Health (1985) *Technical Report: Hazard Assessment of the Electronic Component Manufacturing Industry*, US Department of Health and Human Services, Cincinnati, OH

National Toxicology Program (2000) *Toxicology and Carcinogenesis Studies of Gallium Arsenide (CAS No. 1303-00-0) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies)* (NTP Technical Report 492), Research Triangle Park, NC

Nishiyama, Y., Yamamoto, Y., Fukunaga, K., Satoh, K. & Ohkawa, M. (2002) Ga-67 scintigraphy in patients with breast lymphoma. *Clin. nucl. Med.*, **27**, 101–104

Ohyama, S. Ishinishi, S., Hisanaga, A. & Yamamoto, A. (1988) Comparative chronic toxicity, including tumorigenicity, of gallium arsenide and arsenic trioxide intratracheally instilled into hamsters. *Appl. organometall. Chem*., **2**, 333–337

Omura, M., Hirata, M., Tanaka, A., Zhao, M., Makita, Y., Inoue, N., Gotoh, K. & Ishinishi, N. (1996a) Testicular toxicity evaluation of arsenic-containing binary compound semiconductors, gallium arsenide and indium arsenide, in hamsters. *Toxicol. Lett*., **89**, 123–129

Omura, M., Tanaka, A., Hirata, M., Zhao, M., Makita, Y., Inoue, N., Gotoh, K. & Ishinishi, N. (1996b) Testicular toxicity of gallium arsenide, indium arsenide and arsenic oxide in rats by repetitive intratracheal instillation. *Fundam. appl. Toxicol*., **32**, 72–78

Petrick, J.S., Ayala-Fierro, F., Cullen, W.R., Carter, D.E. & Aposhian, H.V. (2000) Monomethylarsonous acid (MMA^{III}) is more toxic than arsenite in Chang human hepatocytes. *Toxicol. appl. Pharmacol*., **163**, 203–207

Petrick, J.S., Jagadish, B., Mash, E.A. & Aposhian, H.V. (2001) Monomethylarsonous acid (MMA^{III}) and arsenite: LD_{50} in hamsters and in vitro inhibition of pyruvate dehydrogenase. *Chem. Res. Toxicol.*, **14**, 651–656

de Peyster, A. & Silvers, J.A. (1995) Arsenic levels in hair of workers in a semiconductor fabrication facility. *Am. ind. Hyg. Assoc. J*., **56**, 377–383

Pierson, B., Van Wagenen, S., Nebesny, K.W., Fernando, Q., Scott, N. & Carter, D.E. (1989) Dissolution of crystalline gallium arsenide in aqueous solutions containing complexing agents. *Am. ind. Hyg. Assoc. J*., **50**, 455–459

Radabaugh, T.R., Sampayo-Reyes, A., Zakharyan, R.A. & Aposhian, H.V. (2002) Arsenate reductase II. Purine nucleoside phosphorylase in the presence of dihydrolipoic acid is a route of reduction of arsenate to arsenite in mammalian systems. *Chem. Res. Toxicol*., **15**, 692–698

Recapture Metals (2003) *High Purity Gallium: Product Specifications*, Blanding, UT (http://www.recapturemetals.com; accessed 19.09.2003)

Requena, E., Laserna, J.J., Navas, A. & Sánchez, F.G. (1983) Pyridine-2-aldehyde 2-furoylhydrazone as a fluorogenic reagent for the determination of nanogram amounts of gallium. *Analyst*, **108**, 933–938

Rosner, M.H. & Carter, D.E. (1987) Metabolism and excretion of gallium arsenide and arsenic oxides by hamsters following intratracheal instillation. *Fundam. appl. Toxicol*., **9**, 730–737

Sabot, J.L. & Lauvray, H. (1994) Gallium and gallium compounds. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 12, New York, John Wiley & Sons, pp. 299–317

Salgado, M., Bosch Ojeda, C., García de Torres, A. & Cano Pavón, J.M. (1988) Di-2-pyridyl ketone 2-furoylhydrazone as a reagent for the fluorimetric determination of low concentrations of gallium and its application to biological samples. *Analyst*, **113**, 1283–1285

Sampayo-Reyes, A., Zakharyan, R.A., Healy, S.M. & Aposhian, H.V. (2000) Monomethylarsonic acid reductase and monomethylarsonous acid in hamster tissue. *Chem. Res. Toxicol*., **13**, 1181–1186

Sanchez Rojas, F. & Cano Pavón, J.M. (1995) Spectrofluorimetric determination of gallium with N-(3-hydroxy-2-pyridyl)salicylaldimine and its application to the analysis of biological samples. *Anales de Quimica*, **91**, 537–539

Sasaki, T., Kojima, S. & Kubodera, A. (1982) Changes of ^{67}Ga-citrate accumulation in the rat liver during feeding with chemical carcinogen 3′-methyl-4-dimethylaminoazobenzene. *Kaku Igaku*, **19**, 201–208 (in Japanese)

Scansetti, G. (1992) Exposure to metals that have recently come into use. *Sci. total Environ.*, **120**, 85–91

Sheehy, J.W. & Jones, J.H. (1993) Assessment of arsenic exposures and controls in gallium arsenide production. *Am. ind. Hyg. Assoc. J.*, **54**, 61–69

Shiobara, Y., Ogra, Y. & Suzuki, K.T. (2001) Animal species difference in the uptake of dimethylarsinous acid (DMA^{III}) by red blood cells. *Chem. Res. Toxicol.*, **14**, 1446–1452

Sikorski, E.E., McCay, J.A., White, K.L., Jr, Bradley, S.G. & Munson, A.E. (1989) Immunotoxicity of the semiconductor gallium arsenide in female B6C3F1 mice. *Fundam. appl. Toxicol*., **13**, 843–858

Styblo, M., Del Razo, L.M., LeCluyse, E.L., Hamilton, G.A., Wang, C., Cullen, W.R. & Thomas, D.J. (1999) Metabolism of arsenic in primary cultures of human and rat hepatocytes. *Chem. Res. Toxicol.*, **12**, 560–565

Styblo, M., Del Razo, L.M., Vega, L., Germolec, D.R., LeCluyse, E.L., Hamilton, G.A., Reed, W., Wang, C., Cullen, W.R. & Thomas, D.J. (2000) Comparative toxicity of trivalent and pentavalent inorganic and methylated arsenicals in rat and human cells. *Arch. Toxicol*., **74**, 289–299

Ureña, E., Garcia de Torres, A., Cano Pavón, J.M. & Gómez Ariza, J.L. (1985) Determination of traces of gallium in biological materials by fluorometry. *Anal. Chem.*, **57**, 2309–2311

Ureña Pozo, M.E., Garcia de Torres, A. & Cano Pavón, J.M. (1987) Simultaneous determination of gallium and zinc in biological samples, wine, drinking water, and wastewater by derivative synchronous fluorescence spectrometry. *Anal. Chem.*, **59**, 1129–1133

Vahter, M. (1999) Methylation of inorganic arsenic in different mammalian species and population groups. *Science Progress*, **82**, 69–88

Vahter, M. (2002) Mechanisms of arsenic biotransformation. *Toxicology*, **181–182**, 211–217

Versieck, J. & Cornelis, R. (1980) Normal levels of trace elements in human blood plasma or serum. *Anal. chim. Acta*, **116**, 217–254

Wafer Technology Ltd (1997) *MSDS for Gallium Arsenide*, Milton Keynes [http://www.wafertech.co.uk/msds/msds_gaas.html]

Webb, D.R., Sipes, I.G. & Carter, D.E. (1984) *In vitro* solubility and *in vivo* toxicity of gallium arsenide. *Toxicol. appl. Pharmacol.*, **76**, 96–104

Webb, D.R., Wilson, S.E. & Carter, D.E. (1986) Comparative pulmonary toxicity of gallium arsenide, gallium(III) oxide, or arsenic(III) oxide intratracheally instilled into rats. *Toxicol. appl. Pharmacol*., **82**, 405–416

Webb, D.R., Wilson, S.E. & Carter, D.E. (1987) Pulmonary clearance and toxicity of respirable gallium arsenide particulates intratracheally instilled into rats. *Am. ind. Hyg. Assoc. J.*, **48**, 660–667

Welch, B.M., Eden, R.C. & Lee, F.S. (1985) GaAs digital integrated circuit technology. In: Howes, M.J. & Morgan, D.V., eds, *Gallium Arsenide*, New York, John Wiley & Sons, pp. 517–573

Wildfang, E., Zakharyan, R.A. & Aposhian, H.V. (1998) Enzymatic methylation of arsenic compounds. V. Characterization of hamster liver arsenite and methylarsonic acid methyltransferase activities *in vitro*. *Toxicol. appl. Pharmacol.*, **152**, 366–375

Wildfang, E., Radabaugh, T.R. & Aposhian, H.V. (2001) Enzymatic methylation of arsenic compounds. IX. Liver arsenite methyltransferase and arsenate reductase activities in primates. *Toxicology*, **168**, 213–221

Winchell, H.S., Sanchez, P.D., Watanabe, C.K., Hollander, L., Anger, H.O. & McRae, J. (1970) Visualization of tumors in humans using ^{67}Ga-citrate and the Anger whole-body scanner, scintillation camera and tomographic scanner. *J. nucl. Med.,* **11**, 459–466

Wolff, R.K., Kanapilly, G.M., Gray, R.H. & McClellan, R.O. (1984) Deposition and retention of inhaled aggregate $^{67}Ga_2O_3$ particles in beagle dogs, Fischer-344 rats, and CD-1 mice. *Am. ind. Hyg. Assoc. J*., **45**, 377–381

Wolff, R.K., Griffith, W.C., Jr, Cuddihy, R.G., Snipes, M.B., Henderson, R.F., Mauderly, J.L. & McClellan, R.O. (1989) Modeling accumulations of particles in lung during chronic inhalation exposures that lead to impaired clearance. *Health Phys*., **57**, 61–68

Woods, J.S. & Fowler, B.A. (1978) Altered regulation of mammalian hepatic heme biosynthesis and urinary porphyrin excretion during prolonged exposure to sodium arsenate. *Toxicol. appl. Pharmacol.*, **43**, 361–371

Yalcin, S. & Le, X.C. (2001) Speciation of arsenic using solid phase extraction cartridges. *J. environ. Monitoring*, **3**, 81–85

Yamauchi, H., Takahashi, K. & Yamamura, Y. (1986) Metabolism and excretion of orally and intraperitoneally administered gallium arsenide in the hamster. *Toxicology*, **40**, 237–246

Yamauchi, H., Takahashi, K., Mashiko, M. & Yamamura, Y. (1989) Biological monitoring of arsenic exposure of gallium arsenide- and inorganic arsenic-exposed workers by determination of inorganic arsenic and its metabolites in urine and hair. *Am. ind. Hyg. Assoc. J.*, **50**, 606–612

Yu, C., Cai, Q., Guo, Z.-X., Yang, Z. & Khoo, S.B. (2003) Inductively coupled plasma mass spectrometry study of the retention behavior of arsenic species on various solid phase extraction cartridges and its application in arsenic speciation. S*pectrochimica Acta, Part B,* **58**, 1335–1349

Zakharyan, R., Wu, Y., Bogdan, G.M. & Aposhian, H.V. (1995) Enzymatic methylation of arsenic compounds: Assay, partial purification, and properties of arsenite methyltransferase and monomethylarsonic acid methyltransferase of rabbit liver. *Chem. Res. Toxicol.*, **8**, 1029–1038

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. & Mortelmans, K. (1992) Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. mol. Mutagen.*, **19** (Suppl. 21), 2–141