Committee for Risk Assessment

(RAC)

Opinion

Proposing harmonised classification and labelling at Community level in relation to carcinogenicity of

gallium arsenide

ECHA/RAC/A77-O-0000001412-86-05/F

Adopted

1 December 2011

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON GALLIUM ARSENIDE IN RELATION TO CARCINOGENICITY

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation),

the Committee for Risk Assessment (RAC) has adopted an opinion on whether new or relevant information concerning the carcinogenicity of gallium arsenide and its transformation products would change the opinion already adopted on 25 May 2010 (Annex 1), recommending appropriate harmonised classification of gallium arsenide (CAS No. 1303-00-0) as carcinogenic Cat. 1A, according to the CLP Regulation.

I PROCESS FOR ADOPTION OF THE OPINION

Following a request on 10 December 2010 from the European Commission to ECHA, the Executive Director of ECHA in a mandate dated 18 February 2011 (attached as Annex 2) asked RAC to evaluate whether any new or relevant information concerning the carcinogenicity of gallium arsenide and its metabolic products have been received during public consultation launched on 11 March 2011 with a deadline for comments on 27 April 2011.

II ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Marianne van der Hagen

Co-rapporteur, appointed by RAC: Normunds Kadikis

The RAC opinion on carcinogenicity was adopted by consensus on 1 December 2011. It complements the RAC opinion of 25 May 2010 in relation to the proposal for harmonised classification and labelling of gallium arsenide.

III RAC OPINION

RAC has formulated its opinion on whether there is new or relevant information concerning the carcinogenicity of gallium arsenide and its transformation products for deciding on the appropriate harmonised classification of gallium arsenide. The opinion was based upon the information provided in the public consultation limited to carcinogenicity.

Based on all available data and by applying read-across to arsenic and arsenic compounds releasing common metabolites, RAC considered in its opinion of 25 May 2010 that gallium arsenide should be classified as carcinogen Cat. 1A (Regulation EC No. 1272/2008[1]) and carcinogen Cat. 1 (Directive 67/548/EEC).

After the assessment of the information submitted during the new public consultation, the Committee considered that several of the studies submitted were new and relevant for the harmonised classification of gallium arsenide.

[1] 'The CLP Regulation'

Taking into account this new and relevant information, the Committee recommends that gallium arsenide be classified as carcinogen Cat. 1B with the hazard statement H350 (May cause cancer) according to Regulation EC No. 1272/2008[1] and carcinogen Cat. 2, R45 according to Directive 67/548/EEC[2].

The Committee further considered the possibility of classifying differently for the various physical forms of gallium arsenide and for the different exposure routes. However, RAC concluded that there were insufficient grounds to justify this.

The recommended classification of gallium arsenide for all assessed hazard classes is given below in Table 1.

[2] 'The DSD Directive'

Table 1 OPINION OF RAC

Taking into account the RAC opinion adopted on 25 May 2010 and the revision of the carcinogenicity classification proposed in this opinion, RAC considers that **gallium arsenide** should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
	Gallium arsenide	215-114-8	1303-00-0	Carc. 1B[1] Repr. 1B STOT RE 1	H350 H360F[2] H372 (respiratory and haematopoietic system[3])	GHS08 Danger	H350 H360F[2] H372 (respiratory and haematopoietic system[3])			

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	Gallium arsenide	215-114-8	1303-00-0	Carc. Cat. 2; R45 Repr. Cat. 2; R60 T; R48/23	T R: 45-48/23-60 S: 53-45		E

[1] This is the only hazard class covered by this opinion.
[2] It is the view of RAC that the hazard statement H360F is the most appropriate, given the available toxicological profile of gallium arsenide, but RAC recognised that H360 could be applied if the available criteria are applied strictly.
[3] The hazard statement has been corrected by deleting the reference to testes.

IV SCIENTIFIC GROUNDS FOR THE OPINION

A Executive Summary

a) Assessment of information submitted in the public consultation

Extensive amounts of information were provided mainly by manufacturers as well as by producers in the semiconductor industry. The comments and information received covered the following areas: technology, applications, manufacture, use, exposure, occupational epidemiology, relevance of animal experiments on metabolism, carcinogenicity and bioavailability, toxicokinetics (ADME), effects from fine particulate matter, mechanisms for carcinogenicity and the potential existence of a threshold, as well as the read-across approach. The comments were accompanied by reference to more than 200 published scientific papers.

During the discussion after the public consultation had closed, several theoretical considerations on the particulate nature of GaAs used in the different experimental studies were received. These issues were considered relevant for the evaluation of bioavailability of the GaAs particles.

b) Overall conclusion on the classification of gallium arsenide as carcinogenic

Taking as a basis the opinion adopted by the Committee on 25 May 2010 and after reviewing the new and relevant information submitted in the public consultation, as well as considerations provided during subsequent discussions, RAC recommends that gallium arsenide (CAS No. 1303-00-0) is classified as a Category 1B carcinogen with the hazard statement H350 (May cause cancer) according to the CLP Regulation and as carcinogen Cat. 2; R45 according to Directive 67/548/EEC.

Comments received during the public consultation in relation to reproductive toxicity are not addressed in this opinion as agreed at RAC-16[6].

B Background to the opinion

B1 Comments received in the public consultation

Comments were received mainly from industry (IND) and two Member States. A list of interested parties who submitted comments may be found in Annex 4. The comments and the RAC response to them may be found in the RCOM document (Annex 5).

B2 Hazard versus risk – classification versus risk assessment

Several comments received concerned issues of potential risk to human health. According to comments from IND the use of arsenic as a component of gallium arsenide in semiconductor manufacturing does not pose a threat to the human health or the environment due to the closed system manufacturing and the stringent manufacturing controls in place in semiconductor factories using gallium arsenide: “The use of GaAs as a semiconductor wafer material is stringently monitored and highly regulated. There is also no arsenic exposure potential for the consumer during the use phase of the final electronic product, e.g. a mobile phone. The concentration of GaAs components in a semiconductor chip is very low.”

In general, process equipment operators and process equipment service technicians have the greatest potential for chemical exposure. These professionals work in so-called ‘clean rooms’ in the semiconductor facilities. According to the open literature it is not possible to estimate exposure to specific chemicals for individuals due to rapid change in use of various chemicals over time, virtually unique to this industry. Established or suspected carcinogens used in the

[6]RAC-16 minutes: http://echa.europa.eu/documents/10162/17090/rac_meeting_16_minutes_final_en.pdf

semiconductor industry are ionizing radiation, asbestos, arsenic and arsenic compounds, chromium compounds, sulphuric acid mist, ultraviolet light, trichloroethylene, carbon tetrachloride, nickel, and antimony trioxide (Beall et al., 2005).

According to many definitions given in the literature devoted to risk management in a broader sense we must distinguish between hazard and risk. Hazard is something which has the ability to cause harm (anything that can cause harm). In its turn, risk is the likelihood of that harm actually occurring (chance that somebody will be harmed by the hazard). A toxic chemical that is hazardous to human health does not constitute a risk unless humans are exposed to it. It is the likelihood of harm due to exposure that distinguishes risk from hazard.

Several epidemiological studies from the microelectronic industry show that there is not a significant exposure within the whole production process of semiconductors. As a result, the risk is negligible in the particular mode of application of GaAs, although this does not exclude the potential hazard of the substance. RAC stresses the difference between the assessment of the hazard properties of GaAs and risk assessment following exposure during the usage of GaAs in the microelectronic industry. Classification and labelling according to the criteria in the CLP Regulation deals with the assessment of hazard and not risk evaluation in a particular manufacturing process.

Hazard assessment constitutes the first stage of the process of risk assessment. An assessment of the hazards linked to the intrinsic properties of a substance must not be limited in the light of specific circumstances of use, and is carried out regardless of the place where the substance is used, the route by which contact with the substance might arise and the possible levels of exposure to the substance.

B3 Manufacture and Use

According to the information provided by IND, gallium arsenide is used in many high tech applications because of its unique characteristics. It forms a core substrate for semiconductor technology in circuitry, *inter alia,* in mobile phones, CD-players, satellite communications or microwave point-to-point links. Gallium arsenide also demonstrates potential in opto-electronics for application in medical systems and especially in high brightness light emitting diodes (LED) and laser diodes.

B4 Exposure, biomonitoring and epidemiological carcinogenicity studies in workers exposed to arsenic in the semiconductor industry

A number of cancer incidence and (cancer) mortality studies of cohorts of semiconductor workers which were submitted by IND in the public consultation are considered relevant (see Annex 3):

Exposure studies are also available and were cited in the epidemiological studies submitted in the public consultation (Herrick et al., 2005 cited in Beall et al., 2005 and Bender et al., 2007; Marano et al, 2005 cited in Boice et al., 2010). These exposure studies were used to assign the workers to various work groups which later were used in the epidemiology studies described below. The exposure studies demonstrate low levels of arsenic/arsenicals and corresponding metabolites in occupational settings and in workers in the semiconductor industry. Estimates of employees´ exposure to established and suspected carcinogens were not developed (Beall et al., 2005). The studies were not specific to single chemical agents like arsenic or gallium arsenide. Workers in the clean rooms of the semiconductor industry have the greatest exposure to arsenicals and other substances, when compared to other workers in this industry.

Several epidemiological studies in workers exposed to arsenic in the semiconductor industry were cited in the public consultation (Bender et al., 2007; Beall et al., 2005; Boice et al., 2010

and Nichols and Sorahan, 2005). The studies were published in peer reviewed papers and are summarised in Annex 3. They show no overall increased in cancer mortality or from any specific type of cancer that could be related to exposure to gallium arsenide. A study recently published in a report from HSE in UK was also cited (Darnton et al., 2010). The study did not reproduce the findings in the study of McElvenny et al., 2003, who reported an inconclusive two-fold increase in lung cancer incidence among the current and former employees of the same company (National Semiconductor (UK) Ltd., Greenock).

Airborne arsenic levels in the semiconductor industry (chip-making plants) were reviewed by Park et al. (2010). During normal operating activities the weighted arithmetic mean (WAM) was 1.6 µg/m^3 (n=77), whilst during maintenance the WAM was 7.7 µg/m^3 (n=181). The highest level of exposure (WAM = 218.6 µg/m^3) was associated with various maintenance works performed inside an ion implantation chamber. The studies from ion implantation operations reported by Park et al. (2010) were: Wade et al. (1981), McCarthy (1984), Ungers and Jones (1986), Jones (1988), Baldwin et al. (1988), Peyster and Silvers (1995), Hwang and Chen (2000), Hwang et al. (2002), and Chen (2007). Park et al. concluded that for the purpose of future epidemiological studies, ion implantation workers could be divided into operators with potential for low levels of exposure and maintenance engineers with high exposure levels.

Studies indicate that semiconductor workers are exposed to low levels of arsenic as the levels of arsenic compounds in urine is low (Farmer and Johnson, 1990; Morton and Leese, 2010; Morton and Mason, 2006; Yamauchi et al., 1989).

The metabolites DMA (dimethylated arsenicals) can be present in the urine as a result of occupational exposure to inorganic arsenic but also be present due to dietary intake of seafood. For that reason, urinary levels of inorganic arsenic and MMA (monomethylated arsenicals) - rather than DMA - may more correctly reflect exposure to inorganic arsenic, according to Morton and Leese (2010).

The urinary sum of species of As (V), As (III), MMA, DMA was 5.9 µg/g creatinine in UK semiconductor industry workers (n=14) exposed to arsenic used as arsine gas in the doping of chips to enhance the conduction of the silicon or germaniun crystal, and 4.4 µg/g creatinine in the controls (Farmer and Johnson, 1990). DMA was the major single species excreted (97.6 %): As (V) 2.8 µg/g creatinine, As (III) 2.0 µg/g creatinine, MMA 1.4 µg/g creatinine, and DMA 22.2 µg/g creatinine.

In a recent study Morton and Leese (2010) reported analyses of urine from semiconductor/electronics worker (n=65) showing that mean levels of excretion were not significantly different from controls of As (III) 0.1 µg/g creatinine (0.1 µg/L), As (V) 0.2 µg/g creatinine (0.2 µg/L), DMA (V) 3.5 µg/g creatinine (2.8 µg/L), MMA (V) 0.6 µg/g creatinine (0.7 µg/L), and dietary arsenobetaine (AB) 28.8 µg/g creatinine (36.8 µg/L). The workers in this study were not significantly exposed to arsenic. Morton and Mason (2006) reported (n=46) urinary levels in the semiconductor industry where arsenic is used in the form of arsine gas (AsH_3, i.e. As (III)) to produce gallium arsenide, which is subsequently used as a semi-conductor material in electronic circuits. Urinary levels in the workers were significantly higher than controls for all arsenic species except MMA and AB. The levels of As (III) were 2 µg/L and the levels of As (V) 3.6 µg/L, opposed to 0.2 and 1.2 µg/L in the controls (all values 90th percentiles). For DMA and MMA the levels were 9.6 and 1.9 µg/L respectively. The relative amounts in urine from semiconductor workers were 87.4% AB, 1.2% As (III), 9.7% DMA, 1.4% MMA, and 0.4% As (V) on average.

Yamauchi et al. (1989) measured arsenic species in different groups of Japanese workers in a GaAs plant. The ambient arsenic concentration in the plant ranged from 0.002 – 0.024 mg

As/m^3 in the various departments. Urine was sampled twice a day (before work and after work) for three consecutive days. A slight, but significant increase in inorganic arsenic levels was found in post work urinary samples compared to pre work samples from workers involved in GaAs production or processing. No increase in total arsenic or in DMA (V) was observed, possibly due to dietary contribution to urinary DMA levels.

Table 2 Epidemiological studies of workers exposed to arsenic in the semiconductor industry: urinary concentrations of individual arsenic species.

Reference	Unit (conc. in urine)	As (V)	As (III)	MMA	DMA	Industrial sector
Farmer and Johnson, 1990	µg/g creatinine (maximum values)	2.8	2.0	1.4	22.2	UK semiconductor workers
Morton and Leese (2010)	µg/g creatinine (mean values)	0.2	0.1	0.6	3.5	UK semiconductor/electronics workers
	µg/L	0.2	0.1	0.7	3.8	
Morton and Mason (2006)	µg/L (90^{th} percentiles)	3.6	2	1.9	9.6	UK semiconductor/electronics workers
Yamauchi et al. (1989)	µg As/L (post work)	13.4 (as InAs*)	See previous column	3.72	25.7	GaAs plant workers, processing of GaAs crystals

* inorganic arsenic

In conclusion, no increased risk of cancer from exposure to arsenic or arsenic compounds in the semiconductor industry has been described in the epidemiological studies submitted in the public consultation, apart from one study by McElvenny et al. (2003), which reported increased risk of lung cancer in women. This finding was not reproduced in a follow-up study (Darnton et al. 2010). The exposure studies demonstrate low levels of arsenic/arsenicals and corresponding metabolites in occupational settings and in workers in the semiconductor industry.

B5 Bioavailability and toxicokinetics

The size and shape of the gallium arsenide particles as well as the liberation of its two elements gallium and arsenic may all be of importance for the induction of neoplasms in the respiratory system. Gallium arsenide is found to be carcinogenic in the lungs of female rats after inhalation (NTP, 2000). In addition, there is clear evidence of human carcinogenicity from exposure to arsenic and arsenic compounds (IARC; 2004; Straif et al., 2009). More recently, animal models demonstrating arsenic carcinogenicity have been developed (reviewed by Tokar et al., 2010). However, standard experimental animal testing does not reveal systemic arsenic carcinogenicity, due to the low sensitivity of experimental animals. To assess the carcinogenicity, the release and transformation of arsenic ions was evaluated in light of data on classified and listed arsenic carcinogens (Carc. Cat. 1A in Annex VI of the CLP Regulation) in the RAC opinion adopted 25 May 2010 (Annex 1). This approach has been questioned by IND in the public consultation, especially because the stepwise procedure in the OECD guideline on grouping of chemicals (OECD, 2007) was not applied.

According to the CLP Regulation, Annex I, section 3.6.2.1, table 3.6.1, substances which have carcinogenic potential for humans largely based on human evidence should be classified

into category Carc. 1A. However, classification in this category (or in Cat 1B or 2) is also possible if human evidence is lacking for the substance itself provided that there is tumour data from a structural analogue and that the data is further supported by other important factors such as the formation of common significant metabolites for substances not tested for carcinogenicity (CLP Regulation, Annex I, section 3.6.2.2.7).

The following is a discussion on bioavailability and whether the same arsenic species and transformation products will be released following GaAs exposure as will occur following exposure to other classified carcinogenic inorganic arsenicals. It is important to stress that the data are used in a qualitative assessment, rather than a quantitative way.

The bioavailability was determined based on *in vitro* solubility data as well as on animal studies with exposure to GaAs particles of varying sizes via inhalation or intratracheal instillation. The most relevant data on bioavailability are briefly presented below. Although GaAs has low water solubility, it is more soluble in physiological solutions and the available studies indicate it has a bioavailability of 5-10% following both *in vitro* dissolution and intratracheal instillation, whereas oral bioavailability seems to be considerable lower. Furthermore, measurements of increased levels of arsenic and gallium in tissues (blood and testes) in the rat carcinogenicity study (NTP, 2000) as well as indications of systemic toxicity in the 14-week studies (NTP, 2000) were taken as additional data on bioavailability.

Several of the comments received during the public consultation claim that the bioavailability of GaAs had not been sufficiently documented. Several reports provided by the semiconductor industry claim low or no internal exposure in the working atmosphere of this industry. RAC acknowledges that the human data available indicate that the workplace exposure to GaAs does not significantly increase the body burden of arsenic, but it is difficult to evaluate bioavailability based on the human studies available.

The human data is presented above in section B4.

The most central objection to the RAC evaluation of the studies on bioavailability (RAC opinion adopted 25 May 2010 (Annex 1)), was the possible use of gallium arsenide particles which have a partial destruction of the surface of the crystalline structures. These particles were used in the studies upon which the evaluation of bioavailability rests. RAC re-evaluated the existing information on GaAs bioavailability in light of the comments received. Upon mechanical stress, the crystalline structure of gallium arsenide may be disrupted at the particle surface. The information provided by IND indicates that the release of As ions is low or negligible from intact single crystals (e.g. wafers) in physiological solutions. Thus the bioavailability observed in the experimental studies is likely to be related to a partial disruption of the crystalline structure at the particle surface. A similar disruption of the crystalline structure is assumed to be present at the surface of dust particles generated in the occupational setting.

The following studies were considered in the evaluation of bioavailability in the background document to the opinion on gallium arsenide from 25 May 2010: Webb 1984, Rosner and Carter 1987; Pierson et al., 1989; Yamauchi et al., 1986; NTP, 2000.

Webb et al. (1984) investigated relative solubility of three particle sizes of As_2O_3, GaAs and Ga_2O_3 in various solutions resembling *in vivo* conditions. GaAs was found to be soluble under *in vitro* conditions although considerably less than arsenic trioxide. In addition, in the *in vivo* part of the study, it was shown that the absorption of GaAs was greater following intratracheal instillation than oral exposure. Information received from IND supports the conclusion that the content of amorphous structures was higher in these particles than in particles used in the NTP studies and in the studies by Yamauchi (1986) and Pierson (1989). This is thought to be

reflected by the higher *in vitro* solubility of these particles compared to the particles used in the study by Yamauchi (1986).

Yamauchi et al. (1986) demonstrated that approximately 9% of the arsenic was solubilised following a 5 day incubation of GaAs in 0.1 M phosphate buffer. Approximately half this amount was dissolved during the first 24 hours. In the *in vivo* part of the study it was shown that the urinary excretion of total arsenic following oral exposure amounted to 0.5-0.15% of the doses, indicating that GaAs is only slightly soluble in the gastrointestinal tract. The GaAs particles used in this study measured between 2-40 µm (mean volume diameter: 13.89 µm). Although particles were grounded to reduce their size, this treatment is only considered to affect the crystalline structure at breakage sites.

The study by Pierson et al. (1989) analysed the dissolution of GaAs in artificial lung fluid (Gamble solution). A single crystal of GaAs (circular wafer) was broken into pieces of approximately 1 cm^2. GaAs was shown to dissolve slowly in the artificial lung fluid over a period of several days. The concentrations of As and Ga in solution increased rapidly during day one and then increased more gradually throughout the duration of the experiment (10 days). This was also found at a higher oxidation state at the surface of the GaAs crystal after only one hour of exposure to the Gamble solution. The authors concluded that GaAs dissolved in the artificial lung fluid. An expert opinion provided by IND after the public consultation suggests that most of the As release occurs from the breakage sites (Schenk, 2011).

In a study by Rosner and Carter (1987) it was estimated that 5-10% of arsenic form GaAs particles was systemically available following intratracheal instillation. As these particles resemble those used in the study by Webb (1984), they are also likely to have an elevated content of amorphous structures. This study is important for the evaluation of the transformation of the arsenic absorbed as discussed below.

The bioavailability of GaAs was further supported by measurement of gallium and arsenic in blood and testis in the 2-year inhalation exposure study in rats (NTP, 2000). Following exposure to 1 mg/m^3 of GaAs, gallium was detected in blood and testes at the higher exposure concentrations at levels up to 10 times background levels for blood (0.05 µg/g) and 30 times background for testes (1.5 µg/g). Arsenic was measurable in whole blood at concentrations that were approximately two-fold higher than that of chamber controls. These results clearly show that GaAs is bioavailable. IND has pointed out that fairly small particles were used (Mass Median Aerodynamic Diameter (MMAD) from 0.8 to 1.9 µm). Small particle sizes are generally used in inhalation studies (usually a MMAD between 1-4 µm to ensure that they reach the alveoli). This point is also commented in section B6 (b), 'Carcinogenicity'. However, it is important to note that also larger particles are shown to release As under physiological conditions as demonstrated in the studies by Yamauchi et al. (1986) and Pierson et al. (1989).

Moreover, NTP has conducted a series of toxicity studies as part of the overall toxicity assessment of inhalation exposure to gallium arsenide, that includes whole-body inhalation developmental toxicity studies with 0, 10, 37, or 75 mg/m^3 gallium arsenide in Sprague-Dawley rats and Swiss (CD-1) mice (cited as Battelle 1990c in NTP 2000). The results from these studies are briefly described in the NTP (2000) report, but were not included in the 2010 background document to the RAC opinion as developmental toxicity was neither proposed or evaluated by the dossier submitter. Analysis of the concentrations of As and Ga in maternal rat blood and in the conceptus showed that maternal blood concentrations of arsenic in the rat increased with increasing exposure concentration and duration, and achieved high levels (170 µg/g) at the highest dose (75 mg/m3). Levels in the conceptus increased with advancing

gestation, and by day 20 arsenic was detectable in all exposed groups, but not in the controls. In the rat, arsenic is tightly bound to hemoglobin in the erythrocytes and this is likely to limit placental transfer. Levels of gallium in the maternal blood was low, however, fetal tissue had gallium concentrations greater than those found in maternal blood for all exposed groups. These analyses complement the data from the rat carcinogenicity study (NTP, 2000) and confirm that arsenic and gallium is released following inhalation exposure to GaAs particles. The material used for inhalation was obtained by mechanical treatment possibly leading to the disruption of the surface.

RAC considers the indications of systemic toxicity (haematological and testicular effects) as reported in the NTP 14-week studies (NTP, 2000) to be additional supporting evidence for the bioavailability of GaAs. Results of these studies indicated that exposure of rats and mice to 10 mg/m^3 or higher doses induced a minimal microcytic responsive anemia with an erythrocytosis and increased zinc protoporphyrin/haeme ratios. Microcytic anemia would be consistent with an iron deficiency or iron deficiency-like disorders in which iron was unavailable for the production of haeme. As gallium binds to transferrin and it is known that microcytic anemia may develop in patients treated with gallium nitrate (Chitambar, 2010), RAC considers the occurrence of a mild microcytic anemia at 10 mg/m^3 dose to be indicative of systemic toxicity based on the available data. IND questioned this interpretation and claimed that the systemic effects reported in the NTP-studies are all secondary to chronic lung inflammation and/or hypoxemia. Although chronic inflammation in humans may be associated with iron deficiency, such a general association does not seem to be the case in particle-induced lung inflammation studies in animals. Furthermore, the occurrence of responsive microcytic anemia in juvenile animals, progression of anaemic effects over time, clear dose-response relationship and the fact that there is no evidence that erythropoiesis was disturbed in the animal species tested, all support the interpretation that the anaemic effects are direct systemic effects following repeated inhalation of GaAs.

The data presented above describes the evidence that arsenic is released to a certain extent from GaAs particles under physiological conditions. The following is a brief description of the data indicating that similar arsenic species are formed following exposure to GaAs as in response to exposure to arsenic compounds already classified as carcinogenic to humans. Several of the inorganic and methylated As species identified are generally considered to contribute to the carcinogenicity of arsenic compounds. It is a particular concern that a slow and continuous release of As ions from GaAs particles in the lungs may contribute to lung tumour development as the lung has metabolic capacities (oxidation, reduction, methylation) suggesting that both inorganic As and methylated species will be formed at the target site for carcinogenicity.

The following studies were central to the evaluation of transformation, speciation and distribution of released arsenic: Pierson et al., 1989; Yamauchi et al., 1986; Rosner and Carter, 1987 as well as the review by Carter et al., 2003. The evaluation relies to a large extent on data showing the release of inorganic arsenic and the formation of As(III), As(V), MMA(V) and DMA(V) in experimental studies following exposure to GaAs. The extent of formation of such arsenic species will likely vary for different particles due to the influence of the degree of disruption of the crystalline structure for bioavailability as discussed above.

The study by Pierson et al. (1987) reported that As was oxidised at the surface of the GaAs crystals to a species resembling arsenic trioxide As(III) following dissolution in Gamble fluid. It is thus reasonable to assume that the As released from the GaAs particles is mostly in the oxidised form. Studies in hamsters (of which the study by Rosner and Carter (1987) is the

most informative) support that arsenic ions released from GaAs particles seem to undergo a similar biotransformation as more soluble arsenic compounds.

Hamsters are considered to be a suitable animal model for studies of toxicokinetics since its urinary metabolic profile resembles that of humans following inorganic arsenic exposure. The comparative study of Rosner and Carter (1987) as well as the oral hamster study by Yamauchi et al. (1986) show that there is a wide tissue distribution of arsenic species following exposure to GaAs, but the levels of the different species at the target sites are not known. However, the lung is a target site for arsenic-induced carcinogenesis following both oral and inhalation exposure. Importantly, the lung has metabolic capacities (oxidation, reduction, methylation) suggesting that both inorganic As and methylated species will be formed at the target site.

The study by Rosner and Carter (1987) clearly demonstrates that the arsenic released following intratracheal instillation of GaAs, sodium arsenate and sodium arsenite give rise to similar inorganic (As (III) and As (V)) and methylated arsenic species (MMA and DMA) in the urine of the exposed hamsters. In this paper, and as stated in the review paper by Carter et al. (2003), the profile of arsenic species in urine from GaAs exposed animals resembled that of sodium arsenite exposed hamsters. Industry states that gallium arsenide should not be considered as part of the overall exposure to inorganic arsenic in general and that data on carcinogenicity of arsenite and arsenate are not relevant for GaAs. Several of the objections seem to be related to the mode of action of arsenic carcinogenicity and the assumption that a threshold of effects is high when compared to the small amount that is released from GaAs particles. RAC recognises that there are differences in bioavailability and likely also in tissue levels of the different arsenic species at the target sites. However, these are considered to be quantitative and not qualitative differences. As several arsenic species are considered to act in concert to promote carcinogenesis and the actual levels of the relevant arsenic species at the target site (lung) in humans are not known, it is currently not possible to evaluate potential quantitative differences further.

In conclusion, the degree of bioavailability will depend on exposure route, particle size and the degree to which the crystalline structure has been disrupted at the particle surface. Bioavailability of GaAs seems to be relevant (possibly up to about 5%) following exposure to respirable particles, but is probably lower following oral exposure (less than 1%). Taking into consideration the additional human data and the information on the particulate structure of the GaAs provided by IND, RAC maintains the conclusion that GaAs particles are bioavailable. This conclusion is in line with the CLP Guidance (section 1.3.2) on bioavailability. There is a human health concern from gallium arsenide exposure based on this bioavailability. Furthermore, RAC believes that there is sufficient information showing the systemic release of the same arsenic ions and metabolites following GaAs exposure as following exposure to classified carcinogenic inorganic arsenicals. However, it is important to stress that the data are used in a qualitative assessment and a quantitative assessment of the carcinogenic potency of GaAs has not been performed.

B6 *In vitro* and *in vivo* studies of mutagenicity and carcinogenicity

a) Genotoxicity and cell transformation assays

IND claimed that the genotoxicity studies indicated non-genotoxic action and hence a threshold for arsenic carcinogenicity.

Three genotoxicity studies are available and were assessed in the RAC opinion and background document of 2010. GaAs was not mutagenic in the performed Ames tests and negative in an *in vitro* and an *in vivo* micronucleus test. RAC concluded that the tests available did not warrant a classification of GaAs as mutagenic. Comments from the

European trade Union Institute (ETUI) provided references to a Syrian hamster embryo (SHE) transformation assay with several metal compounds including gallium arsenide. In this study, gallium arsenide produced significant morphological transformation at one or more doses in a dose-responsive manner with a 24-hr exposure (Kerckaert 1996).

Comments from IND provided reference to an unpublished *in vitro* gene mutation (HPRT locus) study in mouse lymphoma cells performed according to OECD guideline 476 (Stone V, 2010). The test article was formulated as an extraction in DMSO and particulate matter was removed from the extraction following 72 hour incubation using a filtration step. The result from this test was negative.

RAC is aware of the vast amount of publicly available information on mutagenicity of other arsenic compounds, but this was not presented by the dossier submitter and therefore not reviewed by RAC for the 2010 opinion.

However, genotoxicity data for inorganic arsenic are presented in several reports/reviews (IARC 2004, Straif et al., 2009). Arsenicals (inorganic and organic arsenic compounds) have not been shown to have mutagenic effects in Ames test. The methylated forms of trivalent arsenic are the only arsenic species that have been shown to cause DNA damage *in vitro*. Arsenicals do not react directly with DNA, but oxidative damage is seen in cells treated with low concentrations of As(III). Kligerman et al. (2007) found that MMAIII and DMAIII were clastogenic in human lymphocytes and caused mutations at the Tk(+/-) locus in mouse lymphoma cells. The dimethylated arsenicals were also spindle inhibitors, suggesting that they may be ultimate forms of arsenic that induce aneuploidy. The mode of action for induction of carcinogenesis is likely complex and several mechanisms have been proposed including oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects and DNA-repair inhibition.

IND has provided a comprehensive evaluation of existing genotoxicity data concerning GaAs and inorganic arsenic. According to IND, the available genotoxicity data on gallium arsenide are too limited and the protocols used may not be suited for fine and poorly soluble particles. IND comments mainly relate therefore to the mechanisms of genotoxicity of arsenic species. IND argues in favour of the presence of a threshold for arsenic genotoxicity, but also states that there is insufficient experimental evidence that this is correct.

In conclusion although inorganic arsenicals and metabolites are considered to act mainly by non-mutagenic mechanisms, a threshold for carcinogenicity has so far not been established.

b) Carcinogenicity

Up to now, gallium arsenide is the only inorganic arsenic compound that has been studied by means of long-term exposure (via inhalation) in 2 species (NTP, 2000). No long-term studies via other exposure routes are available. Several comments were received on the interpretation of these NTP studies. RAC agrees with IND claims that the spontaneous incidence of mononuclear-cell leukemia (MCL)[7] in Fischer F344 rats is so high that this effect should be disregarded. RAC also agrees with IND of the irrelevance to humans of the findings of benign pheochromocytoma of the adrenal medulla, with reference to Greim et al., 2009. The findings of alveolar/bronchiolar neoplasms in female rats were however considered relevant.

IND claimed that the lung tumours observed in the female rats should be considered as secondary to exposure to a particulate compound and not as an indication of a primary carcinogenic effect of gallium arsenide. According to IND, the significant inflammation,

[7] Synonyme LGLL (Large Granular Lymphocyte Leukemia)

hyperplasia and metaplasia caused by the inhalation of gallium arsenide most probably represent the primary toxic effect.

RAC considers that the pulmonary effects observed in rodents are caused by the specific properties of GaAs and is not a "pure particle effect" because GaAs induces lung toxicity and carcinogenicity at doses well below those of more inert particles such as titanium dioxide. It is recognised that the GaAs particles as such are important for the tumourigenicity seen in the female rats. However, the potential contribution to the tumourigenicity of solubilised gallium and arsenic ions cannot be excluded. For the observed tumours in the female rats, the release of arsenic is probably of less importance as rodents have low sensitivity to arsenic toxicity and carcinogenicity.

Comments were also received from IND stating that the conditions in the NTP studies (whole-body exposure, very small particles at concentration causing irritation to the lung) causing carcinogenicity were far above real-life scenarios. However these studies were performed according to test guidelines also with respect to the choice of inhalation concentrations. Thus a maximum tolerated dose (MTD) was determined in the 16 day studies based on findings of alveolar proteinosis. The MTD was used as a basis for choosing the exposure concentrations in the 14-week and 2-year studies. Lung burden was followed throughout the study to determine whether an overload situation was reached. Lung clearance increased at higher concentrations (increases in alveolar macrophages). At no time during the 14-week or 2-year studies were the lungs considered to be in an overload situation. The possibility of some oral intake after whole body exposure cannot be excluded; however the Committee assumes this to be of minor importance compared to the inhaled dose given the low gastrointestinal absorbtion. No data on possible local effects in the gastrointestinal tract after oral intake have been found.

IND stated that a fine particulate matter effect should not be disregarded in the NTP studies. There is no CLP guidance on how to interpret fine particulate matter effects in relation to carcinogenicity classification and no differentiation of effects from gallium arsenide per se or from gallium arsenide as fine particulate matter with low solubility is given in the requirements for classification and labelling.

The mass median aerodynamic particle diameter ranged from 0.9 to 1.3 µm in the 16-day studies, from 0.8 to 1.6 µm in the 14-week studies, and from 0.8 to 1.9 µm in the 2-year studies (NTP, 2000). This is within respirable size (< 10 µm) and above nanosize which is defined to be smaller than100 nanometer, i.e. < 0.1 µm. IND claims rightfully that a substantial part of the exposure will be to particles smaller than the MMAD. No motivation for the choice of particle size is given in the NTP report (NTP, 2000), however it is in accordance with the guideline recommendation of a particle size small enough to reach the alveoli. Inhalation was chosen as the route of administration as this is also the relevant exposure route in workers in the microelectronic industry. No increased cancer risk from exposure to gallium arsenide has been documented in the epidemiological studies received. IND claims that the particle size of gallium arsenide in the working place is far above the particle size used in the NTP studies. For considerations of risk, see section B.2.

In conclusion, RAC confirms its original opinion that the NTP studies were adequately performed to be taken into account in the overall assessment of the carcinogenicity of gallium arsenide.

B7 Comments received after the public consultation and discussions at RAC

At RAC-17 IND stakeholders presented its view on the draft opinion and, in addition to points already raised during the public consultation, raised the issue of the physical form of GaAs. In particular IND explained that GaAs is marketed in a solid crystalline form.

Article 5(1) of the CLP Regulation and section 1.2.2 of the CLP Guidance refer to the term 'reasonably expected use' in relation to hazard classification. Reasonably expected use includes any process, all technical operations/manufacturing activities, any putative consumer contact and all professional and non-professional uses.

Comments were received from IND during RAC-17 questioning the validity of several of the studies used in the evaluation of bioavailability of GaAs. These were the studies by Carter and co-workers (Webb 1984; Webb 1986; Rosner and Carter 1987) as well as the study by Yamauchi (1986). The objections were centred on the following statements from IND:

1) A procedure-related infection in the animals used in the studies by the Carter laboratory

2) The possible use of non-crystalline particles in the studies by the Carter laboratory, and

3) That the NTP studies show that GaAs is not bioavailable. IND claimed that if gallium arsenide is bioavailable (at the 1% level or more), then bladder hyperplasia would have been observed in the NTP studies (16-day and 14-weeks studies).

These comments were received during RAC-17 in the form of two presentations, made by representatives from Eurometaux and Business Europe, and in statements made by CEFIC The three discussion points are addressed below.

1) IND claimed that the mild chronic bronchitis reported in the control rats in the study by Webb et al. (1986) was caused by the intratracheal instillation procedure used and that a similar condition thus was likely for the hamsters used in the study by Rosner and Carter, (1987). However, this statement seems to arise from an apparent misinterpretation of the Webb publication as there were no indications from this study to suggest that the infection was procedure-related and there is thus no reason to assume that the hamsters used in the Rosner and Carter study had a similar infection.

2) IND compared the information on the different GaAs particles used in the studies considered by RAC to evaluate the bioavailability of GaAs. They concluded that the GaAs used by the Carter laboratory in the studies by Webb et al., (1984 and 1986); Rosner and Carter (1987), probably had an amorphous structure and was thus questionable for the purpose of evaluation of bioavailability of the crystalline GaAs registered by IND. The particles used in the studies by Yamauchi (1986) were crystalline, but IND claimed that the grinding procedure was likely to have disrupted the crystalline particulate nature thus explaining the bioavailability shown also in this study. Although ground to reduce particle size, this treatment is only considered to break down the crystalline structure at breakage sites and thus only to a limited extent. The particles used in the NTP (2000) studies, however, were considered relevant by IND. As it is important that the data on bioavailibility are relevant for the GaAs particles formed in the working atmosphere, the Rapporteur/RAC has made a careful re-evaluation of available data as well as the data from IND presented during RAC-17. In the view of RAC, the information provided in the Webb et al., (1984) and the Rosner and Carter, (1987) studies are too limited to conclude on the structural nature of the GaAs particles used. However, the information provided indicates that these particles have a higher content of amorphous structures and a higher bioavailability than the particles used in the other experimental studies (Yamauchi 1986 and NTP, 2000).

3) At RAC-17, IND stakeholders suggested that the apparent lack of bladder hyperplasia in the 16-day and 14-week NTP studies showed that crystalline GaAs was not bioavailable.

IND argued that bladder hyperplasia is observed at low exposure levels in animals following oral exposure to sodium arsenite and should have been observed in the NTP studies after exposure to the higher doses of GaAs. When calculating the internal dose of arsenic following inhalation exposure to the highest dose (75 mg/m^3) of GaAs used in the 14-week study and comparing it with oral exposure and the LOAEL dose (10 ppm) of arsenite in mice (Yokohira et al., 2011) it is evident that the internal dose of arsenic following inhalation exposure to GaAs is below the internal LOAEL value reported for the induction of bladder hyperplasia. This calculation assumes a bioavailability of 5% (see section B5). Thus the absence of bladder hyperplasia in the sub-chronic studies does not indicate lack of bioavailability. It only indicates that the resulting internal exposure did not reach the LOAEL value for bladder hyperplasia.

IV OVERALL CONCLUSION AND COMPARISON WITH THE CRITERIA

Carcinogenicity studies in two species (rats and mice) gave limited evidence of carcinogenicity, as there was clear evidence of carcinogenic activity only in female rats. This is based on increased incidences of benign and malignant neoplasms in the lung after inhalation exposure to low concentrations of gallium arsenide. The criteria for carcinogenicity Cat. 2 (CLP Regulation) are therefore met on the basis of animal data alone. These data are discussed in the RAC opinion and background document of 25 May 2010. No human data for gallium arsenide was available to the Committee, but substantial documentation of carcinogenicity in humans of arsenic and arsenic compounds was available, as evaluated by IARC and briefly discussed in the background document to the 2010 RAC opinion.

There is no persuasive evidence for the carcinogenicity of gallium arsenide in humans. However Annex I of the CLP Regulation, section 3.6.2.2.7 states that "A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors, such as: the formation of common significant metabolites e.g. for benzidine congener dyes".

According to the CLP Regulation, Annex 1, Table 3.6.1 assignment of substances to Category 1A (Known to have carcinogenic potential for humans) is largely based on human evidence. Assignment to Category 1B (Presumed to have carcinogenic potential for humans) is usually largely based on animal evidence. However, according to the CLP Regulation, a substance may also be assigned to Category 1B on a case-by-case basis, after carefully assessing the weight of evidence.

No new experimental data on the bioavailability of gallium arsenide was received in the public consultation; however relevant information on particle structure was documented. As described in Article 5(1) of the CLP Regulation and CLP guidance section 1.2.2, the hazard classification shall consider the forms or physical state in which the substance is placed on the market or it can be reasonably expected to be used. As has been highlighted in the previous paragraphs (see section B6) the degree of bioavailability of gallium arsenide will depend on the exposure route, particle size and the degree to which the crystalline structure has been disrupted at the particle surface.

Common significant inorganic arsenic moieties (AsIII and AsV) are formed as well as methylated metabolites (MMA(V) and DMA(V)), both after dissolution of gallium arsenide in body fluids and after exposure to classified inorganic arsenic compounds. This constitutes a concern for the potential carcinogenicity in humans, therefore gallium arsenide is assigned to Category 1 for carcinogenicity. However the relatively low degree of bioavailability of As from GaAs particles as compared to more soluble arsenic compounds, is considered important by RAC for the classification of GaAs in Category 1B rather than 1A.

The mode of action for the carcinogenicity of gallium arsenide as well as for other arsenic compounds is not well known, even though several mechanisms have been proposed (Straif et al., 2009).

RAC recommends the classification of gallium arsenide as carcinogenic in Cat. 1B – H350 according to the CLP Regulation, based on weighting of the following evidence: release of As ion from GaAs, the formation of common significant metabolites with other arsenic compounds listed as carcinogen category 1A (Annex VI of the CLP Regulation), the solubility and bioavailability of GaAs, and the formation of lung tumours in female rats. The corresponding classification according to Directive 67/548/EEC is Carc. Cat. 2.

No specific concentration limit is warranted as the assessment of the carcinogenicity of gallium arsenide compared to other carcinogenic arsenic compounds is qualitative, rather than quantitative.

Article 23 of the CLP Regulation and Annex I, section 1.3.4.1 state: “metals in massive form, alloys, mixtures containing polymers and mixtures containing elastomers do not require a label according to this Annex, if they do not present a hazard to human health by inhalation, ingestion or contact with skin or to the aquatic environment in the form in which they are placed on the market, although classified as hazardous in accordance with the criteria of this Annex. 1.3.4.2. Instead, the supplier shall provide the information to downstream users or distributors by means of the SDS”. Gallium arsenide is considered to be a semi-metal/metalloid. However, RAC considers that the same provisions should apply to the massive form of gallium arsenide.

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[8] *After the adoption of this opinion an IARC Monograph Volume 100 Part C on "Arsenic, Metals, Fibres, and Dust" was received by ECHA. It is published online: http://monographs.iarc.fr/.*

ANNEXES

Annex 1	RAC Opinion of 25 May 2010 on a dossier proposing harmonised classification and labelling at Community level for gallium arsenide.
Annex 2	Request to the Committee for Risk Assessment for an opinion on gallium arsenide in relation to carcinogenicity (18 February 2011)..
Annex 3	Epidemiological carcinogenicity studies in workers exposed to arsenic in the semiconductor industry.
Annex 4	List of interested parties who submitted comments in the public consultation..
Annex 5	Response to comments document (RCOM) - RAC response to comments received during the public consultation of 11 March to 27 April 2011 on the proposed harmonised classification and labelling as carcinogenic of gallium arsenide

Annex 3 Epidemiological carcinogenicity studies in workers exposed to arsenic in the semiconductor industry

Design	Industry	Country	Study size	Adjusted for confounders	Risk estimate#, (95% confidence interval), no. of observations (IARC tumour sites* - lung, skin[9], urinary bladder, only these reported here)	Reference
Cohort mortality	IBM, Two semiconductor manufacturing facilities (East Fishkill (NY), Burlington (VT)), and one storage device (e.g. hard drives for computers) manufacturing facility (San Jose (CA)	USA	126 836	No	Overall mortality rate SMR 65 (CI=64-67), 6579, all cancers combined SMR 78 (CI= 75-81), 2159, lung cancer SMR 61 (men) SMR 98 (women) No estimates of exposure to specific agents developed within the analysis	Beall et al., 2005
Cohort morbidity, (Cancer incidence study) Additional investigation to the one cited in the previous row.	IBM, Two facilities - one semiconductor manufacturing (East Fishkill (NY), and one electronic storage device manufacturing (San Jose (CA)	USA	89 054	No	At the semiconductor facility - all cancers SIR was 81 (CI=77-85), 1541, SIR increased for some subgroups without consistent evidence of causal association with employment factors. lung cancer SIR 60/57 (men facility EF/SJ), 73/68 (women facility EF/SJ), bladder cancer SIR 93/85 (men + women EF/SJ) No estimates of employees´ exposure developed.	Bender et al., 2007
Cohort mortality (follow-up study)	Semiconductor wafer fabrication industry Two large semiconductor companies with fabrication facilities in 10 cities, five states. 12 300 long-term and short-term	USA	100 081	No, only for internal comparisons not external	No increased cancer mortality overall or from any specific form of cancer. All cancer SMR 0.78 (0.69-0.89) and 0.79 (0.62-0.98) for all clean-room workers and clean-room workers employed ≥10 years. For early fabrication era workers all cancer	Boice et al., 2010[10]

[9] non-melanoma skin cancers (IARC Mono Vol 84)
[10] Exposure data reported by Marano et al. 2010

Annex 3 Epidemiological carcinogenicity studies in workers exposed to arsenic in the semiconductor industry

	personal air samples, >98 % below current OELs, and >50 % below limit of detection				SMR was 0.80 (0.64-0.98). Internal comparison early era workers all cancer RR 1.05 (0.9-1.02).	
Cohort morbidity and mortality study (update, 2nd follow-up study)	A semiconductor factory in West Midlands	UK	1807		SMR 99 (CI= 79-122) males / 74 (CI= 65-85 females), all sites cancer SRR 130 (CI= 95-173) males / 94 (CI= 82-109) females. Elevated morbidity for a number of cancer sites but IARCTarget tumour sites not elevated Detailed work history data were unavailable for analysis.	Nichols and Sorahan, 2005
Published in HSE report. To be published in peer reviewed paper Cohort morbidity and mortality study Nested case-control study of lung cancer and breast cancer Follow-up of McElvenny et al., 2003	National Semiconductor UK Ltd (NSUK)	UK	4388	Cohorts adjusted for deprivation Case-control study adjusted for several confounders	Mortality from malignant neoplasms SMR 43.5 (CI= 22.5-75.9) males / 101 (CI=72.6-136.2) females. All malignant neoplasms SRR 90.2 (69.1-116) 12 in males / 102 (84.9-122) 42 in females Cancer registrations of malignant neoplasms of trachea, bronchus and lung SRR 45.1 (12.3-116) 4 in males / 144 (82.3-234) 16 in females	Darnton et al., 2010
Cohort morbidity and mortality study	National Semiconductor UK Ltd (NSUK)	UK	4388	Cohorts adjusted for deprivation	Mortality from malignant neoplasms SMR 47 (CI= 17-102) males / 110 (CI=69-164) females. All malignant neoplasms SRR 99 (64-147) 25 in males / 111 (83-145) 54 in females	McElvenny et al., 2003

Annex 3 Epidemiological carcinogenicity studies in workers exposed to arsenic in the semiconductor industry

							Cancer registrations of malignant neoplasms of trachea, bronchus and lung SRR 56 (7-202) 2 in males / 273 (136-488) 11 in females

**From Straif et al. (2009): Arsenic and inorganic arsenic compounds. Tumour sites (or types) for which there is sufficient evidence in humans: lung, skin, urinary bladder* (Other sites with limited evidence in humans: kidney, liver, prostate).

Annex 4 List of interested parties who submitted comments in the public consultation

- Gallium Arsenide Industry Team (GAIT) representing several manufacturers and producers in Europe and U.S.*
- ZVEI – German Electrical and Electronic Manufacturers´ Association
- European Photonics Industry Consortium
- European Semiconductor Industry Association (EECA-ESIA)
- Aixtron SE
- European Technology Platform Photonics 21
- European Trade Union Institute (ETUI)
- WirtschaftsVereinigung Metalle, DE
- Wafer Technology Ltd, UK
- MSCAs: UK and DE
- A downstream user from France
- An individual from Italy

*Gallium Arsenide Industry Team (GAIT) consists of representatives of:

- Anadigics, Inc. Astrium (EADS)
- Avago Technologies, Ltd.
- AXT, Inc.
- Azur Space Solar Power GmbH
- Epic Associates
- Freiberger Composite Materials
- IPC
- IQE plc
- OSRAM
- RF Micro Devices, Inc.
- Rockwell-Collins
- Texas Instruments, Inc.
- TriQuint Semiconductor, Inc.
- United Monolithic Semiconductors, GmbH
- WIN Semiconductors Corp.

GAIT has obtained the services of six experts in the toxicology of arsenic compounds and carcinogenicity

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