Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

gallium arsenide

ECHA/RAC/CLH-0000000792-73-03/A1

gallium arsenide

EC number: 215-114-8

CAS number: 1303-00-0

Adopted

25 May 2010

CONTENTS

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Gallium arsenide

EC Number: 215-114-8

CAS number: 1303-00-0

Registration number (s): -

Purity: typically at least 99.9999%

Impurities: no data

Proposed classification based on CLP criteria:

Carc. 1A – H350
Repr. 1B – H360F
STOT RE 1 – H372

Proposed classification based on Directive 67/548/EEC criteria:

Carc. Cat. 1; R45
Repro. Cat. 2; R60
T; R48/23

Proposed labelling based on CLP criteria:

GHS pictograms: **GHS08**, **GHS09** Signal word: **Danger** – Hazard statements: **H350** May cause cancer – **H360F** May damage fertility – **H372** Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure,

Proposed labelling based on Directive 67/548/EEC criteria:

Symbol(s) : T
R-phrases: R45– 48/23 – 60
S-phrases : S53 – 45 – 60

Proposed specific concentration limits (if any): none

Proposed notes (if any): Note E

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Gallium arsenide
EC Name:	Gallium arsenide AsGa
CAS Number:	1303-00-0
IUPAC Name:	Gallium arsenide

1.2 Composition of the substance

Chemical Name:	Gallium arsenide
EC Number:	215-114-8
CAS Number:	1303-00-0
IUPAC Name:	Gallium arsenide
Molecular Formula:	AsGa
Structural Formula:	-
Molecular Weight:	144.64
Typical concentration (% w/w):	At least 99.9999%
Concentration range (% w/w):	-

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	4.1	Grey cubic crystals	IARC, 2006
VII, 7.2	Melting point	4.2	1238°C	IARC, 2006
VII, 7.3	Boiling point	4.3	No data	
VII, 7.4	Relative density	4.4 density	5.3176 g/cm^3	IARC, 2006
VII, 7.5	Vapour pressure	4.6	No data	-
VII, 7.6	Surface tension	4.10	No data	-
VII, 7.7	Water solubility	4.8	Insoluble in water (no values given)	IARC, 2006
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7 partition coefficient	No data	-
VII, 7.9	Flash point	4.11	No data	-
VII, 7.10	Flammability	4.13	No data	-
VII, 7.11	Explosive properties	4.14	No data	-
VII, 7.12	Self-ignition temperature		No data	-
VII, 7.13	Oxidising properties	4.15	No data	-
VII, 7.14	Granulometry	4.5	No data	-
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	4.17	No data	-
XI, 7.16	Dissociation constant	4.21	No data	-
XI, 7.17,	Viscosity	4.22	No data	-
	Auto flammability	4.12	No data	-
	Reactivity towards container material	4.18	No data	-
	Thermal stability	4.19	No data	-

Table 1: Summary of physico- chemical properties

Gallium arsenide has been reported to be soluble in 0.1 M phosphate buffer at pH 7.4 and in Gamble solution (an aqueous solution resembling lung fluid and maintained at pH 7.4) (Webb et al., 1984; Pierson et al., 1989). However, Yamauchi et al. (1986) reported that the solubility of arsenic from gallium arsenide after 5 days was 10% or less in 0.2 M phosphate buffer compared to approximately 70% reported by Webb et al. (1984). Although particle sizes were similar, the authors concluded that the difference may have been due to experimental conditions (vessels and volumes of solvents), (NTP, 2000).

2 MANUFACTURE AND USES

2.1 Identified uses

Microelectronic industry

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 (Harrison, 1986; Webb et al., 1984). The National Institute for Occupational Safety and Health (NIOSH) estimated that in 1981 the microelectronics industry employed approximately 180000 workers in the USA, with over 500 plants manufacturing semiconductors (N.I.O.S.H, 1985).

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

Although the substance itself (with its individually assigned CAS number) is not listed in Annex I, it falls under the group entry 'arsenic compounds, with the exception of those specified elsewhere in this Annex' with the index number 033-002-00-5. Under this group entry Gallium arsenide is classified as T; R23/25 and N; R50-53 (29th ATP, Directive 67/548/EEC)).

3.2 Self classification(s)

No data

4 ENVIRONMENTAL FATE PROPERTIES

Not evaluated in this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Inhalation

species	Dose mg/kg bw,	Duration of treatment/observation period	Observations and remarks	Ref.
Rat F344/N	0.1, 1.0, 10, 37 and 75 mg/m^3 of inhaled gallium arsenide for 6h/d, 5d/w (no information on particle size and purity)	13 weeks	Half-life of clearance from the lung was found to be 17 days for both arsenic and gallium	(Greenspan et al., 1991)[1]
Rat, F344/N, n=10 /sex/dose	0, 0.1, 1, 10, 37, 75 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with total impurities <170 ppm, Mass Mean Aerodynamic diameter (MMAD) range: 0.9-1.3µm)	14 weeks	Lung weights increased with increasing exposure 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. 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 75 mg/m^3 group. Corresponding values for arsenic were 31 and 19 days.	(N.T.P, 2000)

[1] Abstract

Rat, Fischer 344/N, n=50, male and female	0, 0.01, 0.1 or 1 mg/m3 for 6h/day, 5 days per week (purity 99% with total impurities <119 ppm including aluminium 52ppm, silicon 33ppm and calcium14 ppm, MMAD range: 0.8-1.9µm)	105 weeks	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 mg/m^3 (96 days) or 0.01 mg/m^3 (133 days). Lung clearance half-lives of arsenic were similar to those of gallium. 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.	(N.T.P, 2000)
Rat, F344/N, male	10, 30, 100 mg/kg (No information on purity, mean volume particle diameter: 12.7 µm)	14 days post observation	Single intratracheal instillation No gallium detected in the blood and urine at day 14 post exposure at any dosage but gallium was retained in the lungs. Arsenic retention ranged from 17 to 32 % of the doses given while gallium retention ranged from 23 to 42 %.	(Webb et al., 1984)
Rat, F344/N, male	100 mg/kg (Mass purity > 99.99%, mean volume particle diameter: 12.7 µm)	14 days post observation	Single intratracheal instillation Lungs from these rats retained 44% of the dose as gallium and 28% of the dose as arsenic at the end of the 14-day study. Blood arsenic concentrations were 44 ppm (7% of the arsenic dose) while gallium was not detected in blood at this time.	(Webb et al., 1986)

Rat, F344/N, male	100 mg/kg (Mass purity > 99.99%, mean volume particle diameter: 5.82 µm)	14 days post observation	Single intratracheal instillation In a later comparable study, Webb *et al.* (1987), demonstrated that smaller gallium arsenide particles had an increased in vivo dissolution rate and there was increased severity of pulmonary lesions. Clearance from lung was faster for arsenic (half-life, 4.8 days) than for gallium (half-life, 13.2 days).	(Webb et al., 1987)
Syrian Gold Hamster, male, n=4	5 mg/kg (Mean volume particle diameter : 5.8 µm)	1,2 and 4 days after instillation	Single intratracheal instillation Blood arsenic concentrations increased from 0.185 ± 0.041 ppm after day 1 to 0.279 ± 0.021 ppm at day 2 after dosing indicated continuing absorption. 5% of arsenic was excreted in the urine during the first 4 days after gallium arsenide instillation (this value has to be compared to the 48 % of arsenic excreted in the urine 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. 27% 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).	(Rosner and Carter, 1987)
Hamster	7.7 mg/kg (purity >99.9999%, test powder contained 0.02% zirconium and traces of yttrium, mean diameter: 1.32 µm, geometric standard deviation 1.76 µm)	Intratracheal instillation twice a week , 16 time	Serum molar concentration of gallium was 32-times higher than that of arsenic in GaAs-treated hamsters.	(Omura et al., 1996a)

Oral

Species	Dose mg/kg bw,	Duration of treatment/observation period	Observations and remarks	Ref.
Syrian Golden Hamster	10, 100 or 1000 mg/kg, singleadministration (no information on purity)	120 h following administration	Urinary excretion of arsenic was 0.15, 0.11 and 0.05% respectively of the high, medium and low oral doses. Faecal excretion of arsenic was around 80 % of the oral doses.	(Yamauchi et al., 1986)
Rat Wistar, male	500, 1000, 2000 mg/kg, single administration (purity 99.99%)	24h, 7 and 15 day after administration	Blood and heart tissue concentration of gallium and arsenic were found to peak at day 7 post exposure.	(Flora et al., 1997)
Rat Wistar, male	100, 200, 500 mg/kg, single administration (purity 99.99%)	24h, 7 and 15 day after administration	Concentration of gallium and arsenic in blood, liver and kidney were found to peak at days 7 post exposure but continued to increase up to 21 days post exposure in the spleen.	(Flora et al., 1998)

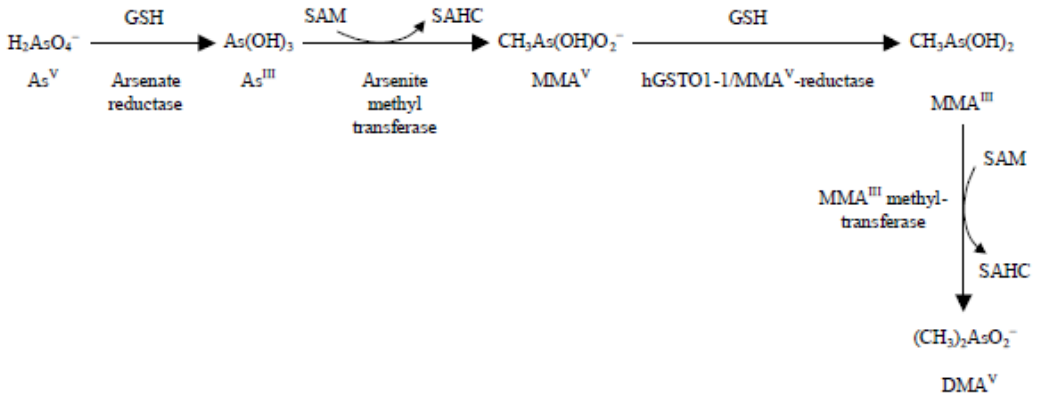
Summary and discussion on toxicokinetics

Gallium arsenide has low solubility in water. However, following in vivo exposure to gallium arsenide, arsenic and gallium is present in both blood and urine to some extent. For gallium, the concentration measured in the testes of rats was 30-fold higher than that of the blood in one study, however still in low concentrations (1.5 µg/g). Webb and co-workers (1984) showed that the rat absorbed about 10% of the arsenic after intratracheal instillation of GaAs at doses ranging from 10 to 100 mg/kg bw, whereas Rosner and Carter (1987) estimated an absorption of about 5-10% of the total dose of arsenic following intratracheal installation of GaAs in hamsters. The urinary excretion data of Yamauchi and co-workers (1986) showed that less than 1% of the total dose of arsenic was excreted following oral administration of hamsters of 10-1000 mg/kg GaAs.

The studies by Yamauchi et al. (1986) and Rosner and Carter (1987) give strength to the assumption of release of the gallium and arsenic moieties from GaAs in mammals, The data are reviewed by Carter et al. (2003).

Biotransformation of inorganic arsenic is relevant for the evaluation of GaAs by read-across to arsenic, as arsenic derived from GaAs is converted into arsenate (where the arsenic atom is present as As^{V}), arsenite (where the arsenic atom is present as As^{III}) and a major metabolite dimethyl arsinic acid as reported in hamsters by Rosner and Carter (1987). The figure below is copied from IARC Vol 84 (2004), the monograph on drinking water contaminated by arsenic.

Figure 3. Biotransformation of inorganic arsenic



Adapted from Zakharyan *et al.* (2001)
The conjugate acids and bases of the several forms of arsenic that are thought to predominate at physiological pH are shown.
SAM, *S*-adenosyl-L-methionine; SAHC, *S*-adenosyl-L-homocysteine; hGSTO1-1, human glutathione-*S*-transferase omega 1-1 (which is identical to MMA^V-reductase)

The two studies presented below have examined the biotransformation and elimination of arsenic following administration of GaAs to hamsters. Hamsters are considered a suitable animal model for such studies since its urinary metabolic profile resembles that of humans following inorganic arsenic exposure. Urine in humans typically contains 10–30% inorganic arsenic, 10–20% MMA, and 60–80% DMA.

The study by Rosner and Carter (1987) compares the metabolism and excretion of arsenic in hamsters after intratracheal instillation of GaAs and the more soluble arsenic oxides, sodium arsenate (As(V)) and sodium arsenite (As(III)). The blood concentrations at 24 hr corresponded to 0.418 ± 0.069 (arsenate), 0.827 ± 0.141 (arsenite), and 0.230 ± 0.056% (GaAs) of the dose administered. The solutions of arsenite and arsenate were almost entirely cleared from the lung by the first day, whereas more than 40% of the dose still remained in the pulmonary region of the respiratory tract 24 hr after GaAs dosing. Four days after GaAs administration, the blood arsenic levels were not significantly lower than after 24 hr, suggesting a continuous absorption phase or steady-state conditions. The GaAs retained in the lungs is a source for a prolonged pulmonary exposure and has the potential for absorption into the systemic circulation during that time. The authors estimated that the absorption of GaAs after 4 days was about one-tenth of that found for arsenite or arsenate. Arsenic absorbed from GaAs was converted to As(III), and As(V), monomethylated arsenicals (MMA^V and MMA^{III}) and dimethylated arsenicals (DMA^V and DMA^{III}). Although the absolute amounts of the arsenic metabolites in the urine of GaAs exposed animals, were much lower than in the urine of animals exposed to the more soluble arsenic oxides, the normalized values, expressed as percentage of total urinary arsenic, showed that the GaAs results were not statistically different from those for arsenite at 48 and 96 hr. In all cases, DMA was the major metabolite. MMA was a minor metabolite for the compounds, accounting for 5-10% of the total urinary arsenic. An unidentified arsenic metabolite accounted for between 2 and 6% of the total dose found in the urine.

Yamauch et al. (1986) showed that following a single administration of 10, 100 or 1000 mg/kg bw of GaAs, the urinary excretion of total arsenic during the 5 day observation time amounted to 0.5-0.15% of the oral doses (inverse dose-response), indicating that GaAs is only slightly soluble in the gastrointestinal tract. The inorganic arsenic released from the orally administered GaAs was converted into inorganic As (In-As; As(III) and/or As(V)), MMA and DMA. In-As accounted for 10-29% and DMA for 54-83% of the urinary excretion of total arsenic. The arsenic concentration in whole blood was slightly elevated following a dose of 100 mg/kg bw of GaAs, and decreased to the control value 72 h. The arsenic concentration in tissues reached a peak at 1 h and 6 h, and was reduced to control levels at 72 h. In-As was found in all organs and tissues examined, while MMA concentration tended to be highest in the kidney, liver and lung, and DMA concentration, in the lung.

In summary the studies with intratracheal instillation of GaAs in rats and hamsters indicate that about 5-10% of the inorganic arsenic in the lungs is systemically absorbed. Furthermore, studies in hamsters following both intratracheal instillation and oral administration shows the conversion of absorbed arsenic to inorganic pentavalent arsenate and trivalent arsenite as well as monomethylated and dimethylated forms. A comparative study suggested that the systemic arsenic released from GaAs was treated like trivalent arsenic in the hamster.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Species	LD50 (mg/kg)	Observations and Remarks	Ref.
Rats (n=5/group)	N.D.[2]	Study not performed according to existing guidelines for acute toxicity. Single oral exposure of finely pulverized GaAs (no information on particle size, purity 99.99%) + 15 d post exposition observation 500, 1000 or 2000 mg/kg Increased blood pressure and heart rate was observed 15 d following single exposure at 2000 mg/kg. Decreased respiration rate was observed 7 and 15 d following single exposure to 2000 mg/kg of GaAs. An inhibition of δ-aminolevulinic acid dehydratase (ALAD) was observed in blood and heart particularly at d7 following exposure to 2000 mg/kg. Urinary δ-aminolevulinic acid (ALA) excretion was elevated only at d7 for all doses.	(Flora et al., 1997)

[2] Not determined

Albino Rats, male (n=30/group)	N.D.	Study not performed according to existing guidelines for acute toxicity. Single oral exposure + 1, 7 or 21 d post-exposition observation. 100, 200, 500 mg/kg (purity 99.99%, no information on particle size) Body weight gain of the exposed groups was lower than that of the control group. δ-aminolevulinic acid dehydratase (ALAD) activity was inhibited in all three GaAs-exposed groups accompanied by elevated urinary excretion of ALA. Increased hepatic levels of malondialdehyde in liver of rats were observed at 200 mg/kg at 7 and 21 d post-exposure and at 500 mg/kg at 21 d post-exposure. Decreased glutathione levels were observed in livers of rats at 200 or 500 mg/kg at 7 d post-exposure. Increased serum aspartate aminotransferase levels were observed 7 d post-exposure in rats exposed to 100, 200 and 500 mg/kg. Dose related decrease of thymus weight was observed at d21 only. Dose dependent decrease of relative spleen weight, spleen cellularity, IgM AFC response was observed at 7 and 21 days.	(Flora et al., 1998)

5.2.2 Acute toxicity: inhalation

No data

5.2.3 Acute toxicity: intratracheal instillation

Species	LC50 (mg/kg)	Observations and Remarks	Ref.
Rat F344/N, male (n=8/group)	N.D.	Single intratracheal instillation of 100 mg/kg GaAs (purity not given, mean count diameter 8.30 µm and mean volume diameter 12.67 µm). No guideline existing for this type of study. Intratracheal instillation of GaAs particulates induced significantly elevated content of lipids, protein and DNA in the lung two weeks after instillation. No effect on body weight or body weight gain (recorded daily). Inflammatory response and pneumocyte hyperplasia was observed in lungs of rats 14 days after intratracheal instillation.	(Webb et al., 1986)

CD Rats, male	N.D.	Single intratracheal instillation of 50, 100 and 200 mg/kg GaAs (purity 99.999%, majority of particles less than 1 µm diameter). No guideline existing for this type of study. A dose-dependent inhibition of blood ALAD was observed six days after treatment with activity decreasing to 5% of controls at the highest dose, with a concomitant marked increase in the urinary excretion of aminolevulinic acid (ALA). Inhibition of blood ALAD following administration of 100 mg/kg of GaAs was maximal (30% of control) 3 to 6 days post exposure and returned to approximately control values on day 18. Urinary excretion of ALA was maximal 3 to 6 days post exposure and recovered toward control values at 18 days. Inhibition of kidney and liver ALAD following 200 mg/kg GaAs exposure was also evident.	(Goering et al., 1988)
B6C3F1 mice, female	N.D.	Single intratracheal instillation of 50, 100 and 200 mg/kg GaAs (purity not given, mean particle size 1.5 µm) No guideline existing for this type of study. .Dose-dependent increased spleen cellularity. Dose dependent decrease of T cells and B cells observed. Dose dependent increase of macrophages observed. The IgM and IgG antibody-forming cell (AFC) response of the spleen to the T-dependent antigen sheep erythrocytes was reduced by 66 and 48% respectively at 200 mg/kg. Treated mice demonstrated a significantly decreased resistance to the B16F10 tumor challenge.	(Sikorski et al., 1989)

B6C3F1 mice, female	N.D.	Single intratracheal instillation of 2.5 to 200 mg/kg GaAs (purity not given, mean particle size 1.5 µm) No guideline existing for this type of study. Dose-dependent decrease in the *in vitro* IgM AFC response to the T-dependent antigen sheep red blood cells (SRBC) with a 97% decrease at 200 mg/kg (compared to control). Dose-dependent decrease of spleen cellularity with a 54% decrease at 200 mg/kg compared to control. 58, 61 and 30 % decrease observed respectively for T cells, B cells and macrophages with no alteration in the percentage of these cells.	(Sikorski et al., 1991b); see also (Sikorski et al., 1991a)

5.2.4 Acute toxicity: dermal

No data

5.2.5 Acute toxicity by other routes: intraperitoneal

Species	LD50 (mg/kg)	Observations and Remarks	Ref.
Mouse	4.7 mg/kg	No information on the protocol of the study, purity or particle size of the material.	(Roshchina, 1966) cited in (N.T.P, 2000)

5.2.6 Summary and discussion of acute toxicity

In the gallium arsenide record from the Hazardous Substance Data Bank, the oral LD50 of GaAs in mice and rats was reported to be greater than 15 g/kg. Furthermore, a dose of 200 mg/kg GaAs has been given to rats by intratracheal instillation without having lethal effects (Williams and Wilkins, 1992). Moreover, no mortality is reported in the oral studies mentioned above for doses up to 2000 mg/kg (Flora et al., 1997; Flora et al., 1998).

After a single intratracheal or oral exposure exposure, gallium arsenide causes dose-dependent systemic suppression of various immune functions, including both humoral and cell-mediated immunity. In addition, single oral or intratracheal exposure to gallium arsenide lead to significant effects on the heme synthesis pathway.

In conclusion, a single administration of gallium arsenide by intratracheal instillation or oral route causes delayed specific haematological and immunological toxicity in a reversible manner (when

further timepoint evaluated). Due to the lack of mortality, a specific acute toxicity classification does not apply. Thus, the group entry for arsenic compounds regarding acute toxicity (R23/25, Directive 67/548/EEC; H301, H331, CLP) does not apply for GaAs and classification as STOT-SE is not warranted.

5.3 Irritation

Not evaluated in this dossier

5.4 Sensitisation

Not evaluated in this dossier

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

No data

5.5.2 Repeated dose toxicity: inhalation

Species	Conc. mg/m^3	Duration of treatment	Observations and Remarks	Ref.
Rat, F344/N, n=10 /sex/dose	0, 1, 10, 37, 75 and 150 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with total impurities <170 ppm, MMAD range: 0.9-1.3µm)	16 days	No guideline existing for this type of study. All rats survived to the end of the study and body weights were similar whatever the group. No clinical findings related to gallium arsenide exposure were observed. Liver and lung weights of males exposed to 1 mg/m^3 or greater or females exposed to 10 mg/m^3 or greater were increased. The thymus weights of all exposed groups of males were decreased. Gallium arsenide particles were visible in the alveolar spaces and, to a lesser extent, within alveolar macrophages of all exposed rats. Moderate proteinosis (surfactant mixed with small amounts of fibrin) and minimal histiocytic cellular infiltrate were observed in the alveoli of all exposed males	(N.T.P, 2000)

			and females and in males exposed to 37 mg/m^3 onward, respectively. Epithelial hyperplasia and squamous metaplasia of the larynx were observed primarly in males exposed to 150 mg/m^3.	
Mouse, B6C3F1, n=10 /sex/dose	0, 1, 10, 37, 75 and 150 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with total impurities <170 ppm, MMAD range: 0.9-1.3µm)	16 days	No guideline existing for this type of study. All mice survived to the end of the study. The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber controls. All males and females in the 75 and 150 mg/m3 groups displayed hypoactivity and abnormal posture. Lung weights of males and females exposed to 10mg/m3 or greater were increased. Gallium arsenide particles were visible in alveolar spaces and macrophages in some mice exposed to 150 mg/m^3. Moderate proteinosis, mild epithelial hyperplasia, and histiocytic infiltration of the lung were observed in males and females exposed to 10 mg/m^3 or greater, and mild chronic inflammation occured in mice exposed to 75 or 150 mg/m^3.	(N.T.P, 2000)
Rat, F344/N, n=10 /sex/dose	0, 0.1, 1, 10, 37, 75 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with total impurities <170 ppm, MMAD range: 0.8-1.6µm)	14 weeks	Study equivalent to guideline OECD 413 except that clinical examination was weekly and not daily, no ophthalmologic examination was performed and spleen weight was not recorded. All rats survived to the end of the study. Mean body weights gains of males in the 37 mg/m^3 and 75 mg/m^3 were significantly less than those of the chamber controls. No clinical findings related to exposure to gallium arsenide were	(N.T.P, 2000)

			observed. Microcytic responsive anemia (in males exposed to 10 mg/m^3 or greater) with an erythrocytosis (from 10 mg/m^3 onward in male and to a lesser extent female) and increase zinc protoporphyrin/heme ratios was observed (on day 23 and at week 14, in a dose-related manner, from 37 mg/m^3 or greater in females and in all treated groups for males). At the end of the study the hemoglobin concentration in blood was reduced by 13 % in males and 1.4 % in female rats in the highest dose group. Increases in platelet (at week 14, in a concentration-related increase, from 37 mg/m^3 or greater in females from 10 mg/m^3 or greater for males) and neutrophil counts (from 10 mg/m^{3}onward), a transient decrease in leukocytes counts, and increases in the serum activities of alanine aminotransferase and sorbitol dehydrogenase were observed. These changes were of greater magnitude in male rats. Lung weights of all exposed groups of rats were increased. Gallium arsenide particles were visible in alveolar spaces and macrophages in the lungs of all exposed rats. Minimal to marked proteinosis and minimal histiocytic cellular infiltration of the alveoli were observed in all exposed groups; minimal squamous metaplasia in the larynx and lymphoid cell hyperplasia of the mediastinal lymph node were observed in males and some females exposed to 37 or 75 mg/m^3. The absolute testis weight of males exposed to 75 mg/m^3 (-55% of	

			controls) and the cauda epididymis (-26 and -38%) and epididymis (-10 and -29%) weights of males exposed to 37 or 75 mg/m^3 were significantly ($p<0.01$) decreased. Body weight of males was decreased only in the 75 mg/m^3 group (-8% of controls). Total spermatid heads per testis and per gram testis and spermatid counts were significantly decreased in males exposed to 75 mg/m^3, while epididymal spermatozoa motility was significantly reduced in males exposed to 10 mg/m^3 or greater with 89.08±1.16 % motility in controls, 81.83±1.03% at 10 mg/m^3, 70.28±2.80% at 37 mg/m^3 and 0.20±0.14% at 75 mg/m^3. No significant differences were noted in the estimated length of the estrous cycle. Testicular atrophy (minimal to marked severity) and epididymal hypospermia (mild to marked severity) was observed in all males exposed to 37 mg/m^3 or greater. Atrophy consisted of decreased thickness of the germinal epithelium of seminiferous tubules due to variable loss of spermatogonia, spermatids and spermatozoa. Hypospermia consisted of decreased numbers of spermatozoa and the presence of cellular debris and large nucleated cells within the lumina of the epididymis.	
Mouse, B6C3F1, n=10 /sex/dose	0, 0.1, 1, 10, 37, 75 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with	14 weeks	Study equivalent to guideline OECD 413 except that clinical examination was weekly and not daily, no ophthalmologic examination was performed and spleen weight was not recorded. One female exposed to 75 mg/m^3	(N.T.P, 2000)

	total impurities <170 ppm, MMAD range: 0.8-1.6µm)		died before the end of the study. Final mean body weights (-10% of controls) and body weight gain of males in the 75 mg/m^3 group were significantly less than the chamber control. The absolute weights of the left testis (-7%, -55% and -57% of controls) , cauda epididymis (-18%, -17% and -16% of controls) and epididymis (-18%, -23% and -31% of controls) were decreased in males exposed to 10, 37, or 75 mg/m^3, respectively. Total spermatid heads per testis and per gram testis and spermatid counts were significantly decreased in males exposed to 37 and 75 mg/m^3. Spermatozoa motility was significantly reduced in males exposed to 37 mg/m^3 or greater with 87.14±1.99 % motility in controls, 82.48±1.66% at 10 mg/m^3, 1.19±0.74% at 37 mg/m^3 and 3.26±1.84% at 75 mg/m^3. The concentration of epididymal spermatozoa were significantly decreased in all exposed groups. No significant differences were noted in the estimated length of the estrous cycle. Exposure related increases in the incidences of testicular atrophy (minimal to moderate severity), epididymal hypospermia (mild to marked severity) was observed in males exposed to 10 mg/m^3 or greater. Lesions were similar to these observed in rats. Exposure related increases of hematopoietic cell proliferation of the spleen, and hemosiderosis of the liver and spleen were observed in groups of male and female mice exposed to 10 mg/m^3 or greater. Exposure to Gallium arsenide affected the circulating erythroid	

			mass and induced a microcytic responsive anemia with an erythrocytosis and increased zinc protoporphyrin/heme ratios in male and female mice exposed to 10 mg/m^3 or greater. At the end of the study the concentration of hemoglobin in the blood was reduced by 5.7 % in both males and females in the highest dose group, and less in the other dose groups. Increases in leukocyte (from 1mg/m^3 for male onward) and neutrophil (from 1mg/m^3 for male and from 10mg/m^3 for female) counts were observed. Lung weights of males exposed to 1 mg/m^3 or greater and females exposed to 10 mg/m^3 or greater were increased. Gallium arsenide particles were visible in alveolar spaces and macrophages in the lungs of mice exposed to 1 mg/m^3 or greater. Mild to marked proteinosis, histocytic infiltration, and epithelial hyperplasia were observed in the alveoli of males and females exposed to 1 mg/m^3 or greater. Minimal to mild suppurative inflammation and granuloma in the lung and squamous metaplasia in the larynx were present in males and females exposed to 10 mg/m^3 or greater. Minimal hyperplasia was observed in the tracheobronchial lymph node of males exposed to 10 mg/m^3 or greater and females exposed to 37 or 75 mg/m^3.	

5.5.3 Repeated dose toxicity: dermal

No data

5.5.4 Summary and discussion of repeated dose toxicity:

Two subacute and 2 subchronic studies on rats and mice by inhalation are reported in the N.T.P report (N.T.P, 2000). Testis atrophy was observed in male rats and mice exposed for 14 weeks. For details, see section 5.8. As in the acute studies, haematological and heme biosynthesis pathway toxicity was observed in rats and mice in the 14 weeks studies. The clinical pathology results of the 14-week studies indicated that exposure of rats and mice to 10 mg/m^3 or higher doses affected the circulating erythroid mass and induced a minimal microcytic responsive anemia with an erythrocytosis and increased zinc protoporphyrin/heme ratios. Microcytic anemia would be consistent with an iron deficiency or iron deficiency-like disorders in which iron was unavailable for the production of heme. For rats, this effect was more pronounced in males than in females. However, the reduction in hemoglobin concentration was considered to be of possible clinical relevance only in male rats (13 % decrease) in the highest dose group, and not in male and female mice.
Moreover, in rats and mice lung (non-neoplastic hyperplasia, metaplasia, granuloma, etc minimal at 1 mg/m^3 sufficiently severe at 10 mg/m^3), non-neoplastic lesions in the larynx of male rats and hyperplasia of the tracheobronchial lymph node in mice warrant a classification as T, R48/23. Converting the concentrations to mg/l (10 mg/m^3 :1000 corresponding to 0.01 mg/litre) and applying the guidance value (C ≤ 0.02) in the table 3.9.2 for particulates in the CLP guidance this corresponds to classification as STOT-RE 1 – H372: Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure.

5.6 Mutagenicity

5.6.1 In vitro data

Test	Cell type	Conc. (mg/l)	Meta-bolic activity	Observations and Remarks	Ref.
Ames	Salmonella typhimurium	10 000 µg/plate	S9 (with and without)	Study performed according to guideline OECD 471. Gallium Arsenide did not induce reversion in strain TA97, TA98, TA100, TA102 or TA1535. S9 was obtained from Aroclor-1254-induced male SD rats or Syrian hamster liver.	(Zeiger et al., 1992) reported in (N.T.P, 2000)

In vitro micronucleus	Syrian hamster embryo cells (1000 binucleated cells analysed to determine the number of micronucleated cells)	2.5, 5, 7.5 and 10 µg/ml	No	No guideline existing for this type of study. No micronuclei induced after a 24-h treatment (respectively 2.0, 2.6, 2.1, 2.6 and 0.2% of micronucleated binucleated cells in DMSO control and at 2.5, 5.0, 7.5 and 10 µg/ml doses GaAs). Colchicine used as a positive control gave an appropriate response (7.2%). (purity and size of particles not given)	(Gibson et al., 1997)

5.6.2 In vivo data

Test	Cell type	Conc. (mg/l)	Meta-bolic activity	Observations and Remarks	Ref.
In vivo micronucleus test	Mouse B6C3F1	75 mg/m3 (inhalation 14 week)		Study performed according to guideline OECD 474 except that no positive control is reported. No micronuclei induced in peripheral blood. (purity >98% with total impurities <170 ppm, Mass Mean Aerodynamic diameter (MMAD) range: 0.9-1.3µm)	(N.T.P, 2000)

5.6.3 Human data

No data

5.6.4 Summary and discussion of mutagenicity

The results of the tests available do not warrant a classification as mutagenic. RAC is aware of the vast publicly available information on mutagenicity of other arsenic compounds, but this was not presented by the dossier submitter and reviewed by the RAC.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

No data

5.7.2 Carcinogenicity: inhalation

Species	Conc. mg/ m^3	Expo. time (h/day)	Durat° of treatmt	Observations and Remarks	Ref.
Syrian Golden Hamster, male, n=33	0 or 0.25 mg/animal (approx. 0.55 µg/kg bw), intratracheal administration (particle size not given)		15 weeks + 111-730 days post observation	Study not performed according to a guideline. Significantly reduced mean survival time in treated group at 1 year (50%) Increased incidence of alveolar cell hyperplasia in treated group (14/30) compared with control (5/30) 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 neoplasm	(Ohyama et al., 1988)
Mouse B6C3F1, n=50, male and female	0, 0.1, 0.5 or 1 mg/m3 (purity 99% with total impurities <119 ppm including alumium 52ppm, silicon 33ppm and calcium14 ppm, MMAD range: 0.8-1.9µm)	6h/day, 5 days per week	105 w (males) 106 w (females)	Study equivalent to guideline OECD 451 except that no blood smear was obtained on animals at 12 months, 18 months and prior to sacrifice. Survival of exposed male and female mice was similar to the chamber controls. Mean body weights of exposed male mice were similar to those of the chamber controls throughout the study; mean body weights of exposed groups of female mice were greater than those of the chamber controls from week 13 until the end of the study. No clinical findings related to gallium arsenide exposure were observed.	(N.T.P, 2000)

				Exposure-related non neoplastic lesions in the lung of all groups of exposed mice: suppurative focal inflammation, chronic focal inflammation, histiocyte cellular infiltration, alveolar epithelial hyperplasia, proteinosis Increased incidences of minimal lymphoid hyperplasia of the tracheobronchial lymph node observed in mice exposed to 1.0 mg/m3 and in 0.5 mg/m3 males No evidence of carcinogenic activity in male or female mice exposed to gallium arsenide	
Rat, Fischer 344/N, n=50, male and female	0, 0.01, 0.1, or 1 mg/m3 (purity 99% with total impurities <119 ppm including alumium 52ppm, silicon 33ppm and calcium14 ppm, MMAD range: 0.8-1.9µm)	6h/day, 5 days per week	105 weeks	Study equivalent to guideline OECD 451 except that no blood smear was obtained on animals at 12 months, 18 months and prior to sacrifice. Survival of exposed male and female rats was similar to the chamber controls. Mean body weights of males exposed to 1.0 mg/m3 were generally less than those of the controls throughout the study Females exposed to 1.0 mg/m3 had slightly lower mean body weights during the second year Incidences of alveolar/bronchiolar neoplasms were significantly increased in females exposed to 1.0 mg/m^3 compared to controls [9/50 (18%) vs. 0/50); These incidences exceeded the historical incidence: 14/1,000 (1.4% ± 1.5%); range, 0% - 4%Exposure-related non neoplastic lesions in the lungs of male and females rats included atypical hyperplasia, alveolar epithelial hyperplasia, chronic active inflammation, proteinosis and alveolar epithelial metaplasia. In the larynx of males exposed to 1.0 mg/m3, the incidences of hyperplasia, chronic active inflammation, squamous metaplasia and hyperplasia of the epiglottis were significantly increased. Incidence of benign pheochromocytoma of the adrenal medulla occured with a positive trend in females rats and was significantly increased in the 1.0 mg/m3 group, exceeding the historical control incidence (27% vs 5.1%) The incidence of mononuclear cell leukemia	(N.T.P, 2000)

				was significantly increased in females exposed to 1.0 mg/m^3 and exceeded the historical control range (66% vs the range 24-47%)	

For transparency the unedited summary table of the 2-year carcinogenesis and genetic toxicology studies of gallium arsenide from the summary NTP report is given below (NTP, 2000):

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Gallium Arsenide				
	Male F344/N Rats	**Female F344/N Rats**	**Male B6C3F$_1$ Mice**	**Female B6C3F$_1$ Mice**
Concentrations in air	0, 0.01, 0.1, or 1.0 mg/m^3	0, 0.01, 0.1, or 1.0 mg/m^3	0, 0.1, 0.5, or 1.0 mg/m^3	0, 0.1, 0.5, or 1.0 mg/m^3
Body weights	1.0 mg/m^3 group generally less than chamber control group	1.0 mg/m^3 group slightly less than chamber control group	Exposed groups similar to chamber control group	Exposed groups generally greater than chamber control group
Survival rates	13/50, 13/50, 15/50, 13/50	19/50, 17/50, 21/50, 11/50	35/50, 38/50, 34/50, 34/50	36/50, 34/50, 31/50, 29/50
Nonneoplastic effects	Lung: hyperplasia, atypical (0/50, 2/49, 5/50, 18/50); alveolar epithelium, hyperplasia (12/50, 16/49, 21/50, 21/50); inflammation, chronic, active (3/50, 43/49, 50/50, 50/50); proteinosis (0/50, 22/49, 50/50, 49/50); alveolar, epithelium, metaplasia (0/50, 2/49, 34/50, 41/50) Larynx: hyperplasia (3/50, 8/50, 4/49, 11/50); inflammation, chronic, active	Lung: hyperplasia, atypical (0/50, 0/50, 9/50, 15/50); inflammation, chronic active (11/50, 46/50, 49/50, 50/50); proteinosis (1/50, 24/50, 47/50, 49/50); alveolar epithelium, metaplasia (0/50, 1/50, 36/50, 41/50)	Lung: inflammation, focal suppurative (0/50, 0/50, 8/50, 23/50); inflammation, chronic, focal (1/50, 3/50, 3/50, 12/50); infiltration cellular, histiocyte (3/50, 10/50, 45/50, 48/50); alveolar epithelium, hyperplasia (4/50, 9/50, 39/50, 45/50); alveolus, proteinosis (1/50, 4/50, 49/50, 50/50) Lymph Node, Tracheobronchial: hyperplasia (5/38, 7/37, 17/40, 24/41)	Lung: inflammation, focal suppurative (0/50, 0/50, 2/50, 14/50); inflammation, chronic, focal (1/50, 2/50, 11/50, 18/50); infiltration cellular, histiocyte (2/50, 13/50, 48/50, 49/50); alveolar epithelium, hyperplasia (2/50, 5/50, 27/50, 43/50); alveolus, proteinosis (0/50, 4/50, 49/50, 50/50) Lymph Node, Tracheobronchial: hyperplasia

	(4/50, 3/50, 4/49, 12/50); metaplasia, squamous (1/50, 2/50, 2/49, 10/50); epiglottis, hyperplasia (0/50, 6/50, 4/49, 5/50)			(10/39, 12/43, 13/42, 23/42)
Neoplastic effects	None	Lung: alveolar/ bronchiolar adenoma (0/50, 0/50, 2/50, 7/50); alveolar/bronchiolar carcinoma (0/50, 0/50, 2/50, 3/50); alveolar/ bronchiolar adenoma or carcinoma (0/50, 0/50, 4/50, 9/50) Adrenal Medulla: benign pheochromocytoma (4/50, 5/49, 6/50, 13/49) Mononuclear Cell Leukemia: (22/50, 21/50, 18/50, 33/50)	None	None
Level of evidence of carcinogenic activity	No evidence	Clear evidence	No evidence	No evidence

Genetic toxicology	
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, TA102, and TA1535, with and without S9
Micronucleated erythrocytes Mouse peripheral blood in vivo:	 Negative

Table 2: From National Toxicology Program, USA: Abstract for TR-492. Toxicology and Carcinogenesis Studies of Gallium Arsenide (CAS No. 1303-00-0) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies)

In female rats who received 1.0 mg/m^3 for two years body weights were slightly less than the control group. As shown in the table above non-neoplastic lung lesions occurred in all exposed groups, with the highest occurrence in the two highest dose groups. At no time during the 14-week or 2-year studies were the lungs considered to be in an overload situation.

5.7.3 Carcinogenicity: dermal

No data

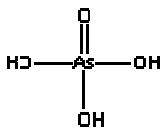
5.7.4 Carcinogenicity: human data

In March 2009 IARC reconfirmed the classification of arsenic and inorganic arsenic compounds as "carcinogenic to humans" (group 1). The working group made the overall evaluation on a group "arsenic and inorganic arsenic compounds" rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism and modes of action of carcinogenicity. The common metabolic pathway of elemental and inorganic arsenic species was underlined: arsenate → arsenite → methylarsonate → dimethylarsenite (IARC, in press; Lancet, 2009).

In Annex VI of the CLP regulation the following arsenic compounds are classified as carcinogens in category 1A:

Index no.	CAS no.	Substance Name
033-003-00-0	1327-53-3	diarsenic trioxide
033-004-00-6	1303-28-2	diarsenic pentaoxide
033-005-00-1	-	arsenic acid[3] and its salts with the exception of those specified elsewhere in this Annex
601-067-00-4	15606-95-8	triethyl arsenate
028-038-00-3	13477-70-8	trinickel bis (arsenate)
082-011-00-0	7784-40-9	lead hydrogen arsenate
601-067-00-4	15606-95-8	triethyl arsenate

[3] AsH_3O_4:



None of the epidemiological studies of cancer in the semiconductor industry were informative with regard to GaAs (IARC, 2006). In the following paragraphs a sample of robust epidemiological studies demonstrating carcinogenicity following exposure to substances yielding metabolites identical to the metabolites identified after exposure to GaAs, is summarized. Diarsenic trioxide (As_2O_3), classified as carcinogen in category 1A (CLP), is metabolized in the body and found as As(III), DMA and MMA in the blood of humans and experimental animals, as is GaAs (described in section 5.1 Toxicokinetics). In drinking water, arsenic in the form of arsenic acid (arsenate, As^V) and arsenous acid (arsenite As^{III}) are assumed to be the causative agents behind the carcinogenicity demonstrated in several epidemiological studies. Arsenic acid and its salts are classified as carcinogens in category 1A (CLP). These salts are also metabolized to DMA and MMA in mammals as shown in figure 3 in section 5.1 Toxicokinetics. The selection of epidemiological studies reported here for smelters and drinking water were made using central studies reported in other review documents (ATSDR, 2007; EFSA, 2009; IARC, 2004). Two studies with moderate to high exposure levels were selected to illustrate the association of drinking water exposure to arsenic with cancer incidence. Several additional high dose studies (e.g. related to bladder cancer) were not included, but these are described in several recent reports as mentioned. For smelters, studies analyzing the cohorts in three copper smelters (2 in USA and 1 in Sweden) were central.

Arsenic in smelters: Arsenic trioxide (diarsenic trioxide, As_2O_3) is classified as carcinogen category 1a (CLP, Annex VI). An association between exposure to arsenic (primarily as arsenic trioxide dust, As_2O_3) in air and respiratory or lung cancer has been reported for several occupationally exposed populations. An outline of some of these studies is given in Table 3. In the Swedish smelter the workers´ cumulative arsenic exposure was reported as less than 0.25 to more than 100 mg/m^3•years. In the smelter in Anaconda (USA) the cumulative arsenic exposure was reported to vary from less than 0.5 to more than 12 mg/m^3•years. In the Tacoma smelter (USA) the cumulative exposure was reported to be in the range from less than 0.75 up to 45 mg/m^3•years. Several of these studies report dose-response curves for respiratory cancer. Smoking and exposure to SO_2 are confounders not always adjusted for in the studies. The level of SO_2 is correlated with the level of arsenic in the smelting process. However it seems probable that smoking habits are independent of exposure to arsenic. In conclusion arsenic emerged as a primary cause of lung cancer in smelter workers after adjusting for cigarette smoking and SO_2 exposure. As_2O_3 is metabolized in the body and found as As(III), DMA and MMA in the blood of humans and experimental animals, as is GaAs.

Table 3. Epidemiologic carcinogenicity studies in workers exposed to As_2O_3 in smelters

Design	Industry	Country	Study size	Adjusted for confounders	Risk estimate#, (95% confidence interval), no. of observations.	Reference
Cohort mortality	Copper smelter workers, Rönnskär	Sweden	3 916	Adjusted for exposure to SO_2	Lung cancer SMR 3.72 (3.04-4.50), ?	Järup et al. 1989
Case-control study within the cohort, (nested case-control), mortality	Copper smelter workers, Rönnskär	Sweden	3 916	Adjusted for smoking and exposure to SO_2	Lung cancer OR range (for increasing cumulative arsenic exposure): 0.7-8.7, 107.	Järup and Pershagen 1991
Cohort, mortality	Copper smelter workers, Anaconda, Montana[4]	USA	1 800[5]	Adjusted for smoking, and exposure to SO_2	Respiratory cancer SMR 1.38-7.04 overall, and 0.89-6.2 for non-smokers, 67.	Welch et al. 1982
Cohort, mortality	Copper smelter workers, Anaconda, Montana	USA	8 045	No	Respiratory cancer, SMR 4.84 in Cohort I, 2.41 in cohort II and 2.25 in cohort III, 262. Overall SMR 2.85, 302.	Lee-Feldstein 1986
Cohort mortality, multistage	Copper smelter workers, Anaconda, Montana	USA	8 014	Adjusted for smoking indirectly	Adjusted excess mortality rate range 0-28 x 10^4 for various age groups, 139.	Brown and Chu, 1983
Cohort, mortality	Copper smelter workers, Tacoma, Washington	USA	2 802	No	Respiratory cancer SMR 1.89 (1.5-2.5), 104.	Enterline and Marsh 1982
Cohort, mortality	Copper smelter workers, Tacoma, Washington	USA	2 802	No	Re-analysis. Respiratory cancer SMR 1.36-3.38, 104.	Enterline et al., June 1987a
Cohort mortality, multistage	Copper smelter workers, Tacoma, Washington	USA	2 802	No	Lung cancer, multistage modeling SMR 1-1.95, 100	Mazumdar et al 1989
Cohort, mortality	Copper smelter	USA	2 802	No	Update of earlier study[6] (Enterline et al.	Enterline

[4] Original cohort study reported by Lee and Fraumeni, 1969

[5] Sample from the 8 045 reported by Lee and Fraumeni, 1969

Table 3. Epidemiologic carcinogenicity studies in workers exposed to As_2O_3 in smelters

	workers, Tacoma, Washington				1987a). Respiratory cancer SMR 2.09 (1.54-3.15), 188.	et al. 1995
Cohort mortality, and nested case-cohort	Workers in 8 copper smelters (the plants in Tacoma and Anaconda were not included in this analysis)	USA	6 078[7]	Adjusted for smoking, and exposure to SO_2	Lung cancer. Relative Risk 0.58-1.60, 70.	Enterline et al.. Oct 1987b

[6] Estimates of exposure 1977-1984 added to previous (1941-1976)

[7] Limited to 5 392 for the analysis of relative risk for lung cancer

Arsenic in drinking water: Inorganic arsenic is found in drinking-water in several parts of the world, mostly in the form of arsenate (As^{V}) and arsenite (As^{III}). Long-term exposure to elevated arsenic concentrations in drinking-water has been shown to be related to increased risks of cancer in the skin, lungs, bladder and kidney (IARC 2004). A few of the studies on arsenic exposure and risk of skin or lung cancers are summarised in Table 4. These studies include groups with a high level of arsenic in their drinking water and a long-time exposure. The studies show that people exposed to elevated levels of arsenic in their drinking water over an extended time period have an increased cancer risk. Moreover, the studies reveal a dose-response trend of ingested arsenic on skin and lung cancer risk and indicate that there is a synergy between cigarette smoking and ingested arsenic on lung cancer risk.

Table 4. Summary of selected epidemiologic studies of inorganic arsenic in drinking water and risk of skin or lung cancer

Design	**Country**	**Study size**	**Adjusted for confounders**	**Comment**	**Concentration µg/L water**	***No. of observations*, Risk estimate#, (95% confidence interval)**	**Reference**
Ecologic	Taiwan	40,421		Incidence of skin cancer was measured as a function of exposure level in over 40,000 people residing in 37 villages, and compared to a control group of 7,500 people with low arsenic exposure. No skin cancers were found in the control group.	0-290 >600	Skin cancer, *428* Prevalence rate (per 1000) Overall prevalence: 10.6 Low concentration: 2.6 High concentration: 21.4	Tseng et al. 1968
Cohort study	Taiwan	10,591	Adjusted for risk factors, including cigarette smoking	Relative risk of lung cancer was related to arsenic exposure level in 2503 residents in southwester and 8088 in Northeastern arseniasis-endemic areas.	≥700 (village median)	Lung cancer, *139* Relative Risk Overall: 3.29 (1.60-6.78), Non-smokers: 2.21 (0.71-6.86)	Chen et al. 2004
Case-control study	Chile	570	Adjusted for risk factors, including cigarette smoking and working in copper smelting industry	Hospital based study using frequency-matched hospital controls. Relative risk of lung cancer was related to arsenic exposure level.	200-400 (average value 1930-94) ≥700 (average concentration 1958-1970; peak exposure period)	Lung cancer, *151* Odds Ratio 8.9 (4.0-19.6) 7.1 (3.4-14.8)	Ferreccio et al. 2000

5.7.5 Summary and discussion of carcinogenicity

Several single listed arsenic compounds have been classified as carcinogenic in humans Category 1A, in EU (CLP regulation annex VI). The entry of elementary arsenic and the generic entry arsenic compounds have not yet been assessed in the EU with respect to carcinogenicity.
Arsenic is assessed by IARC to be a definitive human carcinogen. Animal carcinogenicity data for arsenic is considered either negative or equivocal, probably due to the animal models (Goering et al., 1999). In most animal models animals seem to be less sensitive than humans to the carcinogenic effect of arsenic. However animal studies on DMA, a metabolite of inorganic arsenic, has demonstrated carcinogenicity (Lancet, 2009). No human data is available on carcinogenicity of gallium arsenide. Gallium arsenide was carcinogenic in female rats after inhalation. Based on these findings in animals gallium arsenide fulfil the criteria for classification as Carc. Cat. 3; R40 (Directive 67/548/EEC) and Carc. 2 – H351 (CLP). A specific concentration limit of 0.1 % would be assigned on this basis, because GaAs is a carcinogen of high potency when applying the SCL guidelines. However, the existing knowledge on carcinogenicity from arsenic and arsenic compounds can not be ignored. In 1987 IARC considered "Arsenic and Arsenic compounds" as carcinogenic to humans (Group 1) with a notation that "This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group". In 2006 IARC evaluated gallium arsenide and concluded that there was "inadequate evidence in humans for the carcinogenicity of gallium arsenide" and "limited evidence in experimental animals". Still IARC made an overall evaluation that gallium arsenide is carcinogenic to humans (Group 1). This was based by IARC on the *in vivo* and *in vitro* evidence that gallium arsenide releases gallium and arsenic moieties, and that the observed findings may also be a result of the combination of the two moieties (IARC 2006).

Significantly increased incidences of alveolar/bronchiolar neoplasms, benign pheochromocytoma of the adrenal medulla and mononuclear-cell leukaemia were observed in female rats exposed to the highest concentration. There was no evidence of carcinogenic activity in male rats, nor in male or female mice. No carcinogenic response was revealed in the gallium arsenide instillation study with male hamsters. One possible reason for sex specificity might be a higher retention and lower clearance of gallium arsenide particles from the lung of female rats compared to males (Nikula, 2000).

Established mechanistic events for carcinogenicity from arsenic and inorganic arsenic compounds are oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, DNA-repair inhibition leading to mutagenesis (Lancet, 2009, to be printed as an IARC monograph). No threshold has been identified for the carcinogenic effect of arsenic and it is assumed that the risk of cancer increases linearly with the dose. This is why EPA has applied linear models when estimating lifetime risk (http://www.epa.gov/ncea/iris/subst/0278.htm). IARC has assigned GaAs to group 1 using read-across to arsenic. As an element of the expert judgment, the use of non testing data and read-across is recommended in the CLP regulation and the CLP guidance (see section 3.6.2.3.4 and 3.6.2.1, the latter on carcinogenicity), as well as in the Guidance Document on Information Requirements and Chemical Safety Assessment (GD IR & CSA) R.6: QSARs and grouping of chemicals. Arsenic compounds already listed as carcinogen in category 1A (CLP annex VI) produce the same metabolites in mammals as GaAs. Examples given are arsenate (arsenic acid) in drinking water and diarsenic trioxide from ores processed in copper smelters, where epidemiology demonstrates risk of cancer. Based on read-across to arsenic and other arsenicals GaAs should be classified as carcinogenic category 1A (CLP). This would be in line with

the strong link that exists between CLP and the IARC classification criteria, as discussed in the CLP guidance paragraph 3.6.2.3.1.

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

Species	Dose mg/kg bw/day	Duration of treatment	Observations and Remarks	Ref.
Wistar Rat, n=7 males /group	7,7 mg/kg, twice a week (intratracheal instillation) (purity >99.9999%, test powder contained 0.02% zirconium and traces of yttrium, mean diameter: 1.32 µm, geometric standard deviation 1.76 µm)	8 weeks	No effect on absolute or relative testicular weight. 13% decrease in the relative epididymis weight (not significant) compared to controls (0.222±0.018 vs 0.254±0.025). No significant effect on testis spermatid sperm count. Significant ($p<0.01$) decrease in absolute (199.4±26.7 $x10^6$ vs 266.6±17.0 $x10^6$ in controls) and relative (352.4±48.9 $x10^6$/g vs 438.3±22.0 $x10^6$/g in controls) epididymis sperm count. Significant ($p<0.01$) increase in the proportion of morphologically abnormal sperm of all categories:14.3% of sperm had an immature head (0.4% in controls), 1.3% had teratic head (0.1% in controls) and 4.1% were without a tail (0.9% in controls). Microscopic examination showed no destructive histopathological changes in the seminiferous tubules but concerning degeneration of germ cells, a 40-fold increase was observed in the degenerating late elongated spermatids at the postspermiation stages, stages IX, XI, and XI	(Omura et al., 1996b)

Syrian golden Hamsters, n=8 males /group	7,7 mg/kg, twice a week (intratracheal instillation) (purity >99.9999%, test powder contained 0.02% zirconium and traces of yttrium, mean diameter: 1.32 µm, geometric standard deviation 1.76 µm)	8 weeks	No effect on body weight and body weight gain. No effect on the testis and epididymis weight. Significant ($p<0.01$) epididymal sperm reduction (-22%) was observed in treated animals and this was due to sperm reduction in the body plus tail of the epididymis. No severe tubular changes observed in the testis but spermatid retention at post-spermiation stages (stages IV –VII) was observed. The count of degenerating step 11 spermatid at stages IV-VII was 0.102 $x10^6$/tubule in treated animals vs 0.032 in controls ($p<0.05$).	(Omura et al., 1996a)
Rat, F344/N, n=10 /sex/dose	0, 0.1, 1, 10, 37, 75 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with total impurities <170 ppm, MMAD range: 0.8-1.6µm)	14 weeks	Study equivalent to guideline OECD 413 except that clinical examination was weekly and not daily, no ophthalmologic examination was performed and spleen weight was not recorded. The absolute testis weight of males exposed to 75 mg/m^3 (-55% of controls) and the cauda epididymis (-26 and -38%) and epididymis (-10 and -29%) weights of males exposed to 37 or 75 mg/m^3 were significantly ($p<0.01$) decreased. Body weight of males was decreased only in the 75 mg/m^3 group (-8% of controls). Total spermatid heads per testis and per gram testis and spermatid counts were significantly decreased in males exposed to 75 mg/m^3, while epididymal spermatozoa motility was significantly reduced in males exposed to 10 mg/m^3 or greater with 89.08±1.16 % motility in controls, 81.83±1.03% at 10 mg/m^3, 70.28±2.80% at 37 mg/m^3 and 0.20±0.14% at 75 mg/m^3. The epididymal spematozoal concentration was reduced by 86 % reduction at 75 mg/m^3. No significant differences were noted in the estimated length of the estrous cycle. Testicular atrophy (minimal to marked severity) and epididymal hypospermia (mild	(N.T.P, 2000)

			to marked severity) was observed in all males exposed to 37 mg/m^3 or greater. Atrophy consisted of decreased thickness of the germinal epithelium of seminiferous tubules due to variable loss of spermatogonia, spermatids and spermatozoa. Hypospermia consisted of decreased numbers of spermatozoa and the presence of cellular debris and large nucleated cells within the lumina of the epididymis. At the end of the study, systemic toxicity was reported as microcytic anemia with a decrease in hemoglobin concentration in blood by 13 % in males and 1.4 % in female rats, at 75 mg/m^3. (Other toxicological effects are described in 5.5.2)	
Mouse, B6C3F1, n=10 /sex/dose	0, 0.1, 1, 10, 37, 75 mg/m^3 for 6 hours/day, 5 day/week (purity >98% with total impurities <170 ppm, MMAD range: 0.8-1.6µm)	14 weeks	Study equivalent to guideline OECD 413 except that clinical examination was weekly and not daily, no ophthalmologic examination was performed and spleen weight was not recorded. One female exposed to 75 mg/m^3 died before the end of the study. Final mean body weights (-10% of controls) and body weight gain of males in the 75 mg/m^3 group were significantly less than the chamber control. The absolute weights of the left testis (-7%, -55% and -57% of controls) , cauda epididymis (-18%, -17% and -16% of controls) and epididymis (-18%, -23% and -31% of controls) were decreased in males exposed to 10, 37, or 75 mg/m^3, respectively. Total spermatid heads per testis and per gram testis and spermatid counts were significantly decreased in males exposed to 37 and 75 mg/m^3. Spermatozoa motility was significantly reduced in males exposed to 37 mg/m^3 or greater with 87.14±1.99 % motility in controls, 82.48±1.66% at 10 mg/m^3, 1.19±0.74% at 37 mg/m^3 and 3.26±1.84% at 75 mg/m^3. The concentration of epididymal spermatozoa was significantly decreased in all exposed groups, by 68 % reduction at 10	(N.T.P, 2000)

			mg/m^3 and by 98 % at the mid and high dose. No significant differences were noted in the estimated length of the estrous cycle. Exposure related increases in the incidences of testicular atrophy (minimal to moderate severity), epididymal hypospermia (mild to marked severity) was observed in males exposed to 10 mg/m^3 or greater. Lesions were similar to these observed in rats. At the end of the study, systemic toxicity was reported as microcytic anemia with a decrease in hemoglobin concentration in blood by 5.7 % in both male and female mice. (Other toxicological effects are described in 5.5.2)	

5.8.2 Developmental toxicity

Not evaluated in this dossier.

5.8.3 Human data

No data

5.8.4 Summary and discussion of fertility

No multi-generation studies investigating potential effects of gallium arsenide on fertility are available but repeated dose toxicity studies have reported data on reproductive organs. Several testicular concentration-related modifications, like decreased testis weights, epididymis weights, spermatid counts and spermatozoa motility, have been observed in the whole-body inhalation of gallium arsenide in rats and mice (N.T.P, 2000). For gallium, the concentration measured in the testis of rats was 30-fold higher than that of the blood in one study, indicating a potential for accumulation (see section 5.1 Toxicokinetic). Adverse reduction in epididymal spermatozoal concentration occurred in mice from 10 mg/m^3 (68 % or more) and in rats at 75 mg/m^3 (86 %). Similar testicular effects have also been reported in rats and hamster following intratracheal instillations by Omura (Omura et al., 1996a; Omura et al., 1996b). Finally, histopathologic examination of the testis in rat and hamsters revealed a spermiation failure as spermatid retention was observed at post-spermiation stages for both species. There is clear evidence of testicular toxicity in at least three species and evidence in two species of a site of action of gallium arsenide.

The clinical pathology results of the 14-week studies indicated that exposure of rats and mice to 10 mg/m^3 or higher doses affected the circulating erythroid mass and induced a minimal microcytic

responsive anemia with an erythrocytosis and increased zinc protoporphyrin/heme ratios. For rats, this effect was more pronounced in males than in females. However, the reduction in hemoglobin concentration (5.7 %) was not considered to be of clinical relevance in mice, even at the highest dose. In male rats reduced hemoglobin concentration (13 %) could be of clinical relevance in the highest dose group. The effect on testis is considered to be a primary effect and not viewed as a secondary effect from general toxicity. Toxic effects in lungs were also reported in the 14 weeks studies in rats and mice. However the testicular toxicity reported in these studies is not considered to be a secondary non-specific consequence of the lung toxicity.

The data warrant a classification as Repr. Cat. 2; R60 (Directive 67/548/EEC) and Repr. 1B – H360F (CLP).

5.9 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier

7 ENVIRONMENTAL HAZARD ASSESSMENT

No information on environmental hazards was evaluated in the dossier. However, both in the public consultation and in RAC, the group entry for arsenic compounds in CLP annex VI (Index no. 033-002-00-5) was raised. In this group entry “arsenic compounds, with the exception of those specified elsewhere in this Annex” is classified with regard to aquatic toxicity (acute and chronic).

As no substance specific information is presented, RAC has not evaluated this endpoint and do not propose to carry over the environmental classification from 29th ATP to Directive 67/548/EEC on “arsenic compounds, with the exception of those specified elsewhere in this Annex” (Aquatic acute 1 – H400, Aquatic chronic 1, - H410). However it is understood that industry is conducting relevant studies for the purposes of REACH registration (Eurometaux, pers. Comm.., 2010).

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

The substance has CMR properties justifying a harmonised classification and labelling.

This dossier for harmonisation of the classification of Gallium Arsenide was initially submitted to the Technical Committee on Classification and Labelling (TC C&L) in 2006, although the dossier has never been discussed by this Committee. In this context, full harmonisation was required and all relevant information was therefore collected. Available data indicate that a classification T; R48/23 for repeated toxicity is justified. Moreover, the local lung toxicity observed is likely of importance for the carcinogenic process.

In the absence of the Classification and Labelling Inventory that is not yet available, it is not possible to know what self-classification is applied by manufacturers and importers and if classification for repeated toxicity is adequately applied.

Considering the need for classification for repeated toxicity as shown in this hand-over CLH dossier and the absence of information to confirm its application in industry, action on a community-wide basis is considered to be required to ensure an appropriate and homogeneous application of classification for this endpoint.

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