Annex XV report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **GALLIUM ARSENIDE**

EC Number: 215-114-8

CAS Number: 1303-00-0

Submitted by:	**France**
Date:	**May 2009**
Version:	**2**

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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 Directive 67/548/EEC criteria:

T; R48/23
Repro. Cat. 2; R60
Carc. Cat 3; R40

Proposed classification based on CLP criteria:

STOT Rep. 1 – H372
Repr. 1B – H360F
Carc. 2 – H351

Proposed labelling:

R-phrases: R48/23- R40 – R60
Symbol(s) : T
S-phrases : S45- S53

Proposed specific concentration limits (if any): none

Proposed notes (if any): Note H

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	3.1	Grey cubic crystals	IARC, 2006
VII, 7.2	Melting point	3.2	1238°C	IARC, 2006
VII, 7.3	Boiling point	3.3	No data	
VII, 7.4	Relative density	3.4 density	5.3176 g/cm^3	IARC, 2006
VII, 7.5	Vapour pressure	3.6	No data	-
VII, 7.6	Surface tension	3.10	No data	-
VII, 7.7	Water solubility	3.8	Insoluble in water	IARC, 2006
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	No data	-
VII, 7.9	Flash point	3.11	No data	-
VII, 7.10	Flammability	3.13	No data	-
VII, 7.11	Explosive properties	3.14	No data	-
VII, 7.12	Self-ignition temperature		No data	-
VII, 7.13	Oxidising properties	3.15	No data	-
VII, 7.14	Granulometry	3.5	No data	-
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	No data	-
XI, 7.16	Dissociation constant	3.21	No data	-
XI, 7.17,	Viscosity	3.22	No data	-
	Auto flammability	3.12	No data	-
	Reactivity towards container material	3.18	No data	-
	Thermal stability	3.19	No data	-

Table 1: Summary of physico- chemical properties

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 savwing 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 approximatively 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

Not currently in Annex I

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 alumium 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)

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.	(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 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 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.

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 inhalation or oral route causes delayed specific haematological and immunological toxicity. Due to the lack of mortality, a specific acute toxicity classification does not apply. Moreover, a classification with R39 is not justified.

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. 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 exposed rats. Moderate proteinosis (surfactant mixed with small amounts of fibrin) and minimal histiocytic	(N.T.P, 2000)

			cellular infiltrate were observed in the alveoli of exposed males and females. 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. Lung weights of males and females exposed to 10mg/m3 or greater were increased. Gallium arsenide particles were visible in alveolar spaces and macrohages in some mice exposed to 150 mg/m3. Moderate proteinosis, mild epithelial hyperplasia, and histiocytic infiltration of the lung were observed in males and females exposed to 10 mg/m3 or greater, and mild chronic inflammation occured in mice exposed to 75 or 150 mg/m3.	(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. Microcytic responsive anemia with an erythrocytosis and increase zinc protoporphyrin/heme ratios was observed in exposed groups of rats. Increases in platelet and neutrophil counts, 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	(N.T.P, 2000)

			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 some males and 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 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 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),	(N.T.P, 2000)

			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. Increases in platelet and neutrophil 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). As in the acute studies, haematological and heme biosynthesis pathway toxicity was observed in rats and mice in the 14 weeks studies. These effects cumulated with those observed in the lung (hyperplasia, metaplasia, granuloma, etc.) warrant a **classification as T, R48/23**.

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.

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 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	(N.T.P, 2000)

				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/m3 compared to controls [9/50 (18%) vs 0/50); These incidences exceeded the historical control range (14/1000 = 1.4%) 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 range (27% vs 5.1%) The incidence of mononuclear cell leukemia was significantly increased in females exposed to 1.0 mg/m3 and exceeded the historical control range (66% vs 58%)	(N.T.P, 2000)

5.7.3 Carcinogenicity: dermal

No data

5.7.4 Carcinogenicity: human data

No data

5.7.5 Summary and discussion of carcinogenicity

Significantly increased incidences of alveolar/bronchiolar neoplasms, bening 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, or in male or female mice. No carcinogenic response was revealed in the gallium arsenide instillation study with male hamsters. According to the directive, **the data on animal carcinogenicity of gallium arsenide reported warrant a classification as carcinogenic cat. 3**.

It should be noticed that Gallium Arsenide is considered as carcinogenic to human (Group 1) by IARC as it is included in "Arsenic and Arsenic compounds" group which has been evaluated as IARC group 1, carcinogenic to humans in 1987. A specific evaluation of gallium arsenide was conducted more recently and a conclusion of inadequate evidence in humans and limited evidence in experimental animals has been made (IARC 2006). In fact, there is in vivo and in vitro evidence that gallium arsenide releases gallium and arsenic moieties. Nevertheless, E.U. evaluation of arsenic do not consider arsenic as a carcinogenic substance nor gallium for which data are not as so abundant as for arsenic.

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	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	(Omura et al., 1996b)

	1.76 µm)		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	
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 testies 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,	(N.T.P, 2000)

			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. (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	(N.T.P, 2000)

			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. (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

Several testicular concentration-related modifications, like decreased testis weights, epididymis weights, spermatids counts and spermatozoa motility, have been observed in the whole-body inhalation of gallium arsenide in rats and mice (N.T.P, 2000). 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. Then these data **warrant a classification as Repr. Cat. 2; R60**.

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

Not evaluated in this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

The substance has CMR properties that justify a harmonised classification and labelling for health.

Relevant toxicokinetic data, acute and repeated toxicity data were also reported in this dossier to allow a better understanding of the toxicological profile of gallium arsenide in relationship with the assessment of its CMR properties. These data indicate that a classification T; R48/23 is needed and it is proposed to also add this classification in the harmonised classification of indium phosphide to take advantage of having the information available to the competent expert group.

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