Annex XV report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **INDIUM PHOSPHIDE**

EC Number: 244-959-5

CAS Number: 22398-80-7

Prepared by:	**France**
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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Indium phosphide

EC Number: 244-959-5

CAS number: 22398-80-7

Registration number (s): -

Purity: no data

Impurities: no data

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

Carc. Cat. 2; R45
T; R48/23
Repr. Cat. 3 ; R62

Proposed classification based on CLP criteria:

Carc. 1B – H350
STOT Rep. 1 – H372
Repr. 2 – H361f

Proposed labelling:

R-phrases: R45- R48/23 – R62
Symbol(s) : T
S-phrases : S36/37- S45- S46- 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:	Indium phosphide
EC Name:	Indium phosphide
CAS Number:	22398-80-7
IUPAC Name:	Indium phosphide

1.2 Composition of the substance

Chemical Name:	Indium phosphide
EC Number:	244-959-5
CAS Number:	22398-80-7
IUPAC Name:	Indium phosphide
Molecular Formula:	InP
Structural Formula:	Not applicable
Molecular Weight:	145.8 g/mol
Typical concentration (% w/w):	No data
Concentration range (% w/w):	No data

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	Black brittle crystals with metallic appearance
VII, 7.2	Melting/freezing point	3.2	1062°C
VII, 7.3	Boiling point	3.3	No data
VII, 7.4	Relative density	3.4 density	4.8 g/cm^3
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 (no value available). Slightly soluble in mineral acids. Kabe 1996 reported solubility (as indium) between 100 and 200 µg/L in saline.
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	Flammable in the form of dust when exposed to heat or flame.
VII, 7.11	Explosive properties	3.14	Explosive reaction with dinitrogen tetraoxide + acetonitrile. Violent reaction with mercury (II) bromide at 350°C.
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
	Other		Can react with moisture or acids to liberate phophine (PH_3); when heated to decomposition, it may emit toxic fumes of PO_x.

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

2.1 Manufacture

Indium is mostly obtained from zinc alloys, leached with sulphuric acid to obtain pure metal. Indium can combine with phosphorus to produce a semiconducting compound. A polycrystalline ingot is obtain from melting the compounds at high temperature and high pressure. Then, Czochralski method is used to grow single crystals and ingots are cut into wafers.

2.2 Identified uses

Semiconductor in electronics.

3 CLASSIFICATION AND LABELLING

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

Not currently classified in Annexe 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)

Fischer 344 rats were exposed to particle aerosol of indium phosphide with a mass median aerodynamic diameter (MMAD) of approximately 1.2 µm at 0-1-3-10-30 and 100 mg/m3 for 6h/d, 5d/w for 14 weeks. After 5 days, concentrations can reach 1 mg/g in the lung. 2 weeks after exposure, lung clearance half-life is around 200 days. Indium was also detected in blood and serum at concentrations several orders of magnitude less than that observed in lung tissue. Although blood and serum indium concentrations increased with increasing exposure concentration throughout the 14 weeks of exposure, they appeared to be near steady-state throughout the 16-week recovery period (serum concentrations of 0.315±0.021 µg In/g serum at day 96 of exposure and 0.30±0.05 at postexposure day 112 in animals exposed to 30 mg/m3). Indium was detected in the testis at much higher concentrations than in blood or serum, although still several orders of magnitude less than that in the lung. Similarly, testicular indium concentration increased with increasing exposure concentration and throughout the exposure period. Unlike blood and serum indium concentrations, testicular indium continued to increase in all groups following exposure, indicating that indium was accumulating in the testis over time (concentrations of 0.905±0.081 µg In/g testis at day 96 of exposure and 2.15±0.20 at postexposure day 112 in animals exposed to 30 mg/m3).

Another NTP study performed in mice and rats for 22 weeks confirms lung as a target for indium accumulation. Deposition and clearance follow a zero-order kinetics, or constant rate. The accumulation of indium is proportional to exposure time and concentration. (National Toxicology Program, 2001)

Absorption:

After intratracheal instillation (size of particle not available), a very small proportion of the dose is absorbed: 0,23% of the dose is recovered in urines, whereas a part is retained in tissues and most of the dose must be rejected in digestive ways through muciliary movements in lungs (Zheng et al., 1994).

Intraperitoneal administration of indium phosphide (purity 99.999%, 75% of particles ≤ 2.4 µm in diameter) results in main accumulation in lung and liver (Kabe et al., 1996).

In Syrian golden hamster, InP were administered by intratracheal instillation (purity >99.99%, contains 0.01% zirconium and traces of yttrium, mean count diameter 1.06 µm with geometric standard deviation 1.80). 3mg/kg were given twice a week for 8 weeks. At the end of the exposure period, serum indium concentration were 3.17 µM. Its elimination from serum has a biphasic pattern, with a half-life of 6,2 weeks in the first period and, then, a second half-life of 60 weeks. (Yamazaki et al., 2000)

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

No data

5.2.2 Acute toxicity: inhalation

No data

5.2.3 Acute toxicity: dermal

No data

5.2.4 Acute toxicity: other routes

Species	Doses	Route	LD50 (mg/kg)	Observations and Remarks	Ref.
Rat Fischer 344	0,1.2 , 6 and 62 µg/kg (1µm diameter particles)	intratracheal instillation	> 62 µg/kg	At highest dose and after 8 days, InP induces desquamation of alveolar epithelial cells and pulmonary inflammation revealed by increase in neutrophils and lymphocytes. LDH, total phospholipid and total cholesterol were also increased in broncho-alveolar lavage fluid.	(Oda, 1997)
Rat Ficher 344	0-1,10 and 100 mg/kg (0.8 µm diameter particles)	intratracheal instillation		Markers of the inflammatory response are increased in broncho-alveolar fluid in a dose-dependant manner: neutrophils number, LDH activity, concentration of total proteins, phospholipids and cholesterol. Lungs are infiltrated by neutrophils and macrophages, exude eosinophils and alveolar cells are exfoliated. Macrophages could phagocyte particules of indium phosphide and explain that they are detected in liver and spleen. These organs are deprived of any histopathological sign.	(Uemura, 1997)

5.2.5 Summary and discussion of acute toxicity

No classification is proposed

5.3 Irritation/corrosion

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/l	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Ref.
Rat Fischer 344/N 20 animals/group	0, 1, 3,10, 30 and 100 mg/m^3 (aerosol) (trace impurities <0.2% including arsenic, selenium, antimony and iron > 0.01%; approxi-mate MMAD: 1.2 µm)	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	One male of the high dose group died during the study (no additional details in study report). Body weights decreased in this group. After 14 weeks, features of inflammation are observed in all exposed animals: alveolar proteinosis, interstitial regenerative fibrosis, alveolar cell hyperplasia and inflammatory cells in multiple sites of the lung. More lymphocytes and mononuclear cells were found in bronchial and mediastinal lymph nodes of exposed animals. Hepatocellular necrosis is revealed by increase in alanine aminotransferase and sorbitol dehydrogenase activities in all males and from 10 mg/m^3 in females. Histopathological necrosis lesions of the liver are observed at 100 mg/m^3. Haematopoiesis is stimulated both in bone marrow and in the spleen, consistent with microtic erythrocytosis.	(National Toxicology Program, 2001)

B6C3F1 mice 20 animals/group	0,1, 3, 10, 30 and 100 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	Mice were more affected than rats. In the 100 mg/m^3 group, all animals either died or were removed moribund. In the 30 mg/m^3 group, one male and three females were also removed. In these two groups animals were lethargic and hardly breathed. Animals exposed to 3 mg/m^3 lost weight and body weight at necropsy was 94% of the controls weight. Lungs are discoloured and enlarged. Inflammation is more severe than in rats.	(National Toxicology Program, 2001)
Fischer 344/N rats 60 males and 60 females/group	0-0,03-0,1 and 0,3 mg/ m^3 (aerosol) (trace impurities <0.12% including arsenic, selenium, antimony and iron between 0.01% and 0.02%; approxi-mate MMAD: 1.2 ± 0.1 µm)	6h/d, 5d/w	21 weeks (0,1 and 0,3 mg/ m^3) 105 weeks (0 and 0,03 mg/m^3)	Lung lesions are qualitatively similar but less severe than in the 14-week study. However, because of the severity of the lesions observed after 3 months, treatment also had to be interrupted in rats of 0.1 and 0.3 mg/m^3 groups after 21th week. No death is reported nor during this period, nor later. A chronic inflammation is found in rats. Lung weight is increased 1.6 fold to 2.1 fold in groups exposed to 0,1 and 0,3 mg/ m^3. Areas of inflammation are less spread than in the 14-week study and are predominantly subpleural. An alveolar hyperplasia considered as regenerative has developed in all males and two groups of females. Indium phosphide particules are found in bronchial and mediastinal lymph nodes. Histochemical analysis of tissues suggests that inflammation could by the consequence of oxidative stress and could lead to cancer. Oxidative stress is revealed by a defense enzyme, GST-Pi, but also by oxidative damage in DNA, 8OHdG. Pro-inflammatory and proliferation-inducing enzymes are	(National Toxicology Program, 2001), (Gottschling et al., 2001)

				induced, such as iNOS and COX2. Survival in the 0.03 mg/m^3 group in not affected; abnormal breathing and lethargy are observed after 18 months.	
B6C3F1 mice 60 males and 60 females /group	0-0,03-0,1 and 0,3 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w	21 weeks (0,1 and 0,3 mg/ m^3) 105 weeks (0 and 0,03 mg/m^3)	3 months after beginning of exposure, the administration of InP has to be stopped in the 0.1 and 0.3 mg/m^3 groups because of the severity of lung inflammation. The animals are kept until the end of the experiment. The incidence of proliferative and inflammatory lesions in the lung is increased in all treated groups. Alveolar epithelium is hyperplasic and marked by proteinosis. Pleural fibrosis is found in most of the animals. Indium phosphide particules are found in lungs and in bronchial and mediastinal lymph nodes. At 2 years, the incidence of inflammation of the heart and the arteries of the heart is elevated in treated animals. Survival rates, determined in all groups at the end of the 2-year period, are all decreased. No correlation between exposure and death can be made because of discontinuity of exposure in two groups. Body weights decrease in the 0.03 and 0.3 mg/m^3 groups. Abnormal breathing in the main observed clinical sign.	(National Toxicology Program, 2001)

5.5.3 Repeated dose toxicity: dermal

No data

5.5.4 Other routes: intratracheal instillation

Species	Dose mg/kg/day	Exposure time	Duration of treatment	Observations and Remarks	Ref.
Syrian golden hamster 30 animals per group.	2,25 mg/w (purity > 99.99%, mean count diameter 3.2 µm with geometric standard deviation 2.88)	Once/w	15 w	Body weight and life span are not altered by exposure to InP. Body weight gain was slightly affected. InP particules deposite in lungs around lesions characterized by proteinosis, alveolar or bronchiolar hyperplasia, pneumonia, emphysema and metaplastic ossification. Some of are found in lymph nodes.	(Tanaka et al., 1996)
Syrian golden hamster 45 males 4 to 8 hamsters sacrificed per sampling time	3 mg/kg (purity >99.99%, contains 0.01% zirconium and traces of yttrium, mean count diameter 1.06 µm with geometric standard deviation 1.80)	Twice/w	8 w	Animals were examined after 8, 16, 40, 64 and 88 weeks. No animal died during the administration period. Three animals died of emaciation during the observation period. Body weights were lower in treated animals compared to controls without any sign of systemic toxicity. The difference in body weight was significant after the 8-wk exposure period and remains significant after the 88-wk observation period with a maximum difference around wk 48 where body weight in the treated group was approximately 85% of the control group. At the end of the exposure period, serum indium concentrations were 3.17 µM. Lung weights were significantly increased at all time and lungs were marked by moderate to severe inflammation during the observation period. Indium particles were found in the bronchio-alveolar space and	(Yamazaki et al., 2000)

				alveolar septae. Besides these areas, severe sporadical hyperplasia of bronchio-alveolar cells were noticed. Interstitial fibrosis was reported during the observation period and was still severe at the end of the 88-wk period. Cell proliferation was assessed by immunostaining of proliferating cell nuclear antigen (PCNA). Expression of PCNA was evident on the nuclei of bronchio-alveolar celles, mostly in the localized hyperplastic lesions and sparsely in the severely inflamed areas. It decreased during the observation period but was still significant after 88 weeks. No mutation in any of the K-ras gene was evident in any of the lesions examined The authors suggest that the continuous stimulation by accumulated particles could induce hyperplasia but is not sufficient to induce neoplasia.	

5.5.5 Summary and discussion of repeated dose toxicity:

→ These studies, using inhalation or intratracheal instillation, show that indium phosphide induce severe inflammation in lungs. Particles accumulate in lungs, but can also be found in bronchial and mediastinal lymph nodes. Modification of the anti-oxidative potential of the cells by indium phosphide could lead to different lesions and to hyperproliferation. The proportion of the substance which passes into systemic circulation is unknown, but at higher doses, other organs can be reached, such as liver, where necrosis is observed.

Because of the severe effects (death , moribund condition and hepatic necrosis) observed at 30 and 100 mg/m^3 in mice and/or rats in the 14-week study and at 0,1 and 0,3 mg/m^3 (severe inflammatory lung lesions) during the intermediate period of the 2-year study, **a classification Toxic, R48/23 is proposed.**

5.6 Mutagenicity

5.6.1 In vitro data

No data

5.6.2 In vivo data

Somatic cells

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Ref
Micronucleus	B6C3F1 mice	Peripheral blood	Inhalation 14-week (aerosol similar than in subchronic study)	No significant genetic damage is highlighted by the test.	(National Toxicology Program, 2001)
Point mutations	B6C3F1 mice	Hepatocellular adenoma and carcinoma	2 years (aerosol similar than in chronic study)	Point mutations were assessed in two genes: ß-catenin and H-ras. Frequency of mutations in ß -catenin was increased (4-fold) in hepatocellular neoplasms in exposed animals.	(National Toxicology Program, 2001)

No data on germ cells

5.6.3 Human data

No data

5.6.4 Summary and discussion of mutagenicity

→ No classification required.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

No data

5.7.2 Carcinogenicity: inhalation

Species	Conc. mg/l	Exposure time (h/day)	Observations and Remarks	Ref
B6C3F1 mice 50 animals/group	0-0.03-0.1 and 0.3 mg/m^3 (aerosol) (trace impurities<0.12% including arsenic, selenium, antimony and iron between 0.01% and 0.02%; approximate MMAD: 1.2 ± 0.1 µm)	0,03 mg/m^3 for 2 years, 0,1 and 0,3 mg/m^3 for 21 weeks	Besides inflammation of the lung, adenomas and carcinomas are noticed in mice exposed to InP. It has to be reminded that no dose-effect correlation can be made in the 2-year studies since exposure of the groups 0.03 and 0.1 mg/m^3 were interrupted after 21 weeks. In mice, a clear increase in carcinoma of alveolar and bronchiolar cells is seen in lungs. The following numbers are noticed in control and treated groups of 50 animals in males: 6/15/22/13 and in females: 1/6/5/7. These tumours are characterised by a great anaplasia. Some of them could have spread from the lung into the mediastinum and distant metastases. Mice also develop hepatocellular adenoma and carcinoma, in males (26/40/37/39) and in females (18/28/24/23). A non significant increase in rare neoplasms in the small intestine is noticed in males: there is one adenoma or carcinoma in controls versus 2 to 6 in treated groups.	(National Toxicology Program, 2001)
F344/N rats 50 animals/group	0-0,03-0,1 and 0,3 mg/m^3 (aerosol) (material similar to the mice study)	0,03 mg/m^3 for 2 years, 0,1 and 0,3 mg/m^3 for 21 weeks	In rats, adenoma or carcinoma of alveolar and bronchiolar cells are increased in lungs. The following numbers are noticed in control and treated groups in males: 7/22/30/35 and in females: 1/10/6/26. In F344 rats, pheochromocytome development from adrenal medulla occurs with a low rate. In this study, pheochromocytome incidence is clearly increased in males (10/26/18/24) and less in females (2/6/2/9). The following less significant neoplasms are described in males: skin fibroma (1/4/7/3), mononuclear cell leukemia (16/23/29/25), and in females: mammary	(National Toxicology Program, 2001)

			gland carcinoma (0/8/3/2), mononuclear cell leukemia (04/21/14/24).	
Syrian golden Hamster 30 males	0 or 2,25 mg powder InP (or 1.8 mg In) in phosphate buffer /week (purity > 99.99%, mean count diameter 3.2 µm with geometric standard deviation 2.88)	15 weeks	After exposure, animals are observed for 105 weeks. Inflammatory and hyperproliferative lesions are observed in the lung (9 alveolar or bronchiolar cell hyperplasia in treated animals versus 0 in controls in groups of 23 animals, one squamous cell metaplasia in treated animals versus 0 in controls in groups of 23 animals). 7 animals developed tumours (2 in control group) located in lung, liver, pancreas, adrenal gland or lymph node.	(Tanaka et al., 1996)

5.7.3 Carcinogenicity: dermal

No data

5.7.4 Carcinogenicity: human data

In the only two studies reporting cancer incidence in workers of semiconductors industry, indium phosphide is one of the possible carcinogens (Table 2).

The first study was conducted in the West Midlands in England. In this cohort of 1807 workers, melanoma and non-melanoma skin cancer incidence were increased (2 and 1.5-fold factors). (Sorahan et al., 1992). The cohort was updated in 2005 and the excess of risk skin melanoma was still significant and an excess of risk of rectum cancer was identified (Nichols et al., 2005).

In the second study perform in Scotland in a 4388 workers cohort, an excess (3.9 fold) of lung cancers is found in females; smaller excesses of stomach cancer in women are also noticed. (McElvenny et al., 2003).

Table 2 – Summary of main results in the cancer cohort studies

Cohort description	Estimation of exposure	Cancer site	Risk	Observations and remarks
(Sorahan, 1992) N=1807 workers (1526 women) first employed in or before 1970 at a semiconductor factory, followed up until 1989 for mortality and 1988 for cancer incidence	Information on dates of hire and leaving employment only. Full work histories not known. A wide variety of chemicals was in use at the plant but worker exposure to these chemicals is believed to have been well controlled.	All All Respiratory Skin-melanoma Skin – non-melanoma	SMR=0.72 (95% CI: 0.59-0.87) SRR=0.96 (95% CI: 0.77-1.18) SRR=0.97 (95% CI: 0.48-1.74) SRR=2.00 (95% CI: 0.41-5.84) SRR=1.52 (95% CI: 0.81-2.59)	SMR and SRR were adjusted for socio-economic status. A total of 3 cases of melanoma were reported.
(Nichols, 2005) N=1807 workers (1526 women) first employed in or before 1970 at a semiconductor factory, followed up until 2002 for mortality and 2001 for cancer incidence Reference: general population of England and Wales	Information on dates of hire and leaving employment only. Full work histories not known. A wide variety of chemicals was in use at the plant but worker exposure to these chemicals is believed to have been well controlled.	All neoplasms All malign. neoplasms Respiratory Skin-melanoma Skin – non-melanoma Rectum	SMR=0.77 (95% CI: 0.63-0.92) SRR=1.00 (95% CI: 0.87-1.13) SRR=0.81 (95% CI: 0.53-1.20) SRR=2.17* (95% CI: 1.12-3.79) SRR=1.10 (95% CI: 0.77-1.53) SRR=1.99* (95% CI: 1.20-3.79) *$p<0.05$	SMR and SRR were adjusted for socio-economic status. A total of 12 cases of melanoma and 19 cases of rectum cancer were reported.

(McElvenny, 2003) N=4388 workers (2262 women) employed at a Scottish semiconductor manufacturing facility on or before 30 April 1999, followed up until 2000 for mortality and 1998 for cancer incidence (mean length of follow-up: 12.5 years) Reference: Scottish rates	The only exposure indicator was an identification of individuals who worked in the fabrication areas (51% of males and 79% of females). The following known or suspected carcinogens were also present in the factory: antimony trioxide, arsenical compounds, arsine, asbestos in building, chromium trioxide, kaewool, highly refined mineral oil, sulphuric acid mists, ionizing radiation, UV radiation, krypton 85, cabon tetrachloride, chromic acid, trichloroethane, trichloroethylene	All malignant neoplasms (females) Respiratory (females) Stomach (female) Breast (females) All malignant neoplasms (males) Respiratory (males) Stomach (males)	SMR=110 (95% CI: 69-164) SRR=111 (95% CI: 83-145) SRR=245* (95% CI:122-438) SRR=438 (95% CI:90-1281) SRR=134(95% CI:82-206) SMR=47 (95% CI:17-102) SRR=99 (95% CI: 64-147) SRR=71 (95% CI:15-207) SRR=0 (95% CI:0-441) *p<0.05	SMR and SRR were adjusted based on the Carstairs index of deprivation, which take into account average health profile of the economically deprived areas of Scotland. Female stomach cancer (3 cases observed): all cases were in women aged <50 years and wityh a latency between 5-10 years. Female lung cancer (11 cases): exces was higher in those cases with <10 years latency than for latency > 10 years. Cases had a relatively high age at hire and therefore potential exposures prior employment at the facility. Female breast cancer (20 cases): adjustment with reproductive history was not performed.

5.7.5 Summary and discussion of carcinogenicity

→Two cohort studies on the semiconductor industry are available. Nichols 2005 reports an excess of risk of melanoma and rectum cancer whereas McElvenny 2003 reports a significant excess of lung cancer in women and non-significant excess of stomach and breast cancer in women. Due to the limited size of the two cohorts, the limited information on exposure history and coexposures and the lack of consistency of results between the two cohorts it is not possible to draw a conclusion on the carcinogenic effect of indium phosphide in humans.

In animal studies, tumors of lungs, adrenal gland and other less significant tumours are induced by indium phosphide in mice, rats and hamsters. Development of tumours outside lungs after inhalation exposure suggests that the mechanism does not only rely on a local inflammatory and proliferative effect.
We propose to classify indium phosphide **as Carc. Cat. 2; R45**.
It should be noticed that Indium phosphide is considered as probably carcinogenic to humans (Group 2A) by IARC based on a conclusion of inadequate evidence in humans and sufficient evidence in experimental animals (IARC 2006).

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

No reproductive study has been performed on indium phosphide but some repeated-dose studies report data on reproductive organs and function.

5.8.1.1 Inhalation

Species	Conc. mg/l	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Ref.
Rat Fischer 344/N 20 animals/group	0, 1, 3,10, 30 and 100 mg/m^3 (aerosol) (trace impurities <0.2% including arsenic, selenium, antimony and iron >	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	General toxic effects are described in section 5.5.2. In females, no effect was seen on estrous cycle parameters. Ovarian and uterine atrophy was reported in all females at 100 mg/m3. In males, degenerating cells from testicular germinal epithelium were present within seminiferous tubules in 5/10 males and within epididymi in all males of the 100 mg/m3 group and were considered secondary to debilitation. Cauda epididymis weight was	(National Toxicology Program, 2001)

	0.01%; approxi-mate MMAD: 1.2 µm)			significantly decreased at 30 mg/m3 with a weight of 90% of controls. In this group the body weight was 89% of controls. No significant differences were noted in sperm morphology. Reproductive tissue evaluation and estrous cycle characterization were not performed at 100 mg/m3.	
B6C3F1 mice 20 animals/group	0,1, 3, 10, 30 and 100 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w (week 1 to 4 and 10 to 14) 7d/w (week 5 to 9)	14 weeks	General toxic effects are described in section 5.5.2. Uterine atrophy (decreased uterine horn diameter, stromal condensation, shrunken glands) was observed in 4/10 and 8/10 females administered with 30 and 100 mg/m3, respectively and ovary atrophy (without or with poorly developed corpora lutea) in 9/10 females administered with 30 and 100 mg/m3. These lesions occurred mainly in animals that died before the end of the study and were considered secondary effects. Estrous cycles were longer than 5 five days or unclear in 5/8 animals at 30 mg/m3 and in 1/10 animals in controls. In males, testis weight was significantly decreased at 10 and 30 mg/m3 with a weight of respectively 93 and 91% of control testis weight. In these groups the body weights were respectively 87 and 64% of controls. Cauda epididymis (73% of controls) and epididymis (81% of controls) weights were also significantly decreased at 30 mg/m3. No significant differences were noted in sperm morphology. Reproductive tissue evaluation and estrous cycle characterization were not performed at 100 mg/m3.	(National Toxicology Program, 2001)
Fischer	0-0,03-0,1 and 0,3	6h/d,	21 weeks (0,1 and	General toxic effects are described	(National Toxicolo

344/N rats 60 males and 60 females/group	mg/ m^3 (aerosol) (trace impurities <0.12% including arsenic, selenium, antimony and iron between 0.01% and 0.02%; approxi-mate MMAD: 1.2 ± 0.1 µm)	5d/w	0,3 mg/ m^3) 105 weeks (0 and 0,03 mg/m^3)	in section 5.5.2. No significant histopathological findings were observed in the genital system of males and females. Reproductive tissue evaluation and estrous cycle characterization were not performed.	gy Program, 2001), (Gottschling et al., 2001)
B6C3F1 mice 60 males and 60 females /group	0-0,03-0,1 and 0,3 mg/m^3 (aerosol) (material similar to the rat study)	6h/d, 5d/w	21 weeks (0,1 and 0,3 mg/ m^3) 105 weeks (0 and 0,03 mg/m^3)	General toxic effects are described in section 5.5.2. No significant histopathological findings were observed in the genital system of males and females. Reproductive tissue evaluation and estrous cycle characterization were not performed.	(National Toxicology Program, 2001)

5.8.1.2 Intratracheal instillation

Species	Route	Dose	Exposure time (h/day)	Observations and Remarks	Ref.
Syrian golden hamster 45 males 4 to 8 hamster per	Intra-tracheal instillation (purity >99.99%	3 mg/kg	Twice/w for 8 w	The 8-week exposure period was followed by a 88-week observation period during which animals were periodically sacrificed. Body weight in the treated group was similar to the control group	(Omura et al., 2000)

sampling time	, contains 0.01% zirconium and traces of yttrium, mean count diameter 1.06 µm with geometric standard deviation 1.80)			immediately after the last instillation. A decrease was significant from weeks 16 to 64 after instillation and body weight was 80-90% of controls during this period. Body weight became compatible with the control value again 88 weeks after the last instillation. Weights of testes and epididymis decreased after the exposure period, representing 60-70 % of the control values between the 16th and the 64th week. Values reach control levels during the week 88. Caudal sperm count already decreased significantly immediately after exposure. It further decreased to 40-50% of control values from weeks 16 to 64 after last instillation. 88 weeks after instillation, values became normal again. From weeks 16 to 88 after instillation, 30-50% of seminiferous tubules have histopathologic alterations, whereas expected abnormalities linked to age are observed in 14% of seminiferous tubules in controls at week 88. The increase is statistically significant compared to controls at weeks 16 and 64. Percentage in the treated group would be lower (14.2%) at 88th week if one particularly affected animal was not included. Histologic alterations included degeneration and loss of germ cells, exfoliation and disarrangement of seminiferous epithelium and atrophy of seminiferous tubules but without alteration of spermatogonia.	

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

→ Effect on male genital organs (absolute and relative weight loss of testes and epididymes, decrease in sperm count and histopathological lesions in seminiferous tubules) were observed in hamsters in one study after intra-tracheal instillation of 3mg/kg InP twice a week for 8 weeks. The effects were seen in presence of a decrease in body weight compared to controls. However, the decrease in reproductive organs was more important than the general decrease of body weight. Besides, decrease of caudal sperm count was observed immediately at the end of exposure when no significant decrease of body weight was reported.
Severity of effects increased during the observation period and tends to reverse at the end of the observation period of 88 weeks. This study therefore provides evidence that indium phosphide induces toxic effects on the male reproductive system. Although some generic toxic effects also occurs, reproductive effects is not considered secondary to the generic toxic effects in this study and are therefore relevant for classification.

Interpretation of the study is however limited by the single dose used and the absence of direct assessment of fertility function. But it clearly demonstrates the intrinsic property of indium phosphide to have adverse effect on the male reproductive system. The unusual mode of administration used in this study is not considered to have a significant impact on interpretation of the results compared to inhalation regarding systemic effects such as reproductive effects.

By inhalation, effects on the reproductive systems are seen in rats and mice only at doses inducing massive toxicity in the NTP 14-week studies and no effects were reported in the 2-year studies in which doses were limited up to 0.3 mg/m3.

Toxicokinetic data shows that indium can accumulate in testes after inhalation and raise a concern on potential accumulation of high concentrations due to chronic exposure.

On the basis of effects on male reproductive organs observed in hamsters and of toxicokinetic data showing an accumulation of indium in testis but in the absence of direct assessment of fertility function we propose a classification **Repro. Cat. 3; R62**.

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 effects.

Acute and repeated toxicity data were also reported in this dossier to allow a better understanding of the toxicological profile of indium phosphide 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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