INDIUM PHOSPHIDE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 22398-80-7
Deleted CAS Reg. No.: 1312-40-9, 99658-38-5, 312691-22-8
Chem. Abstr. Serv. Name: Indium phosphide (InP)
IUPAC Systematic Name: Indium phosphide
Synonyms: Indium monophosphide

1.1.2 *Molecular formula and relative molecular mass*

InP Relative molecular mass: 145.79

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Black cubic crystals (Lide, 2003)
(*b*) *Melting-point*: 1062 °C (Lide, 2003)
(*c*) *Density*: 4.81 g/cm^3 (Lide, 2003)
(*d*) *Solubility*: Slightly soluble in acids (Lide, 2003)
(e) *Reactivity*: Can react with moisture or acids to liberate phosphine (PH_3); when heated to decomposition, it may emit toxic fumes of PO_x (ESPI, 1994)

1.1.4 *Technical products and impurities*

No data were available to the Working Group.

1.1.5 *Analysis*

Occupational exposure to indium phosphide can be determined by measurement of the indium concentration in workplace air or by biological monitoring of indium. No analytical

methods are available for determination of indium phosphide *per se.* Determination of phosphorus cannot provide the required information on occupational exposure.

(*a*) *Workplace air monitoring*

The respirable fraction of airborne indium, collected by drawing air through a membrane filter in a stationary or personal sampler, can be determined by nondestructive, INAA. This technique has been applied to the determination of indium concentration in ambient air particulates (Kucera *et al*., 1999). Using irradiation with epithermal neutrons, indium concentrations have also been determined in arctic aerosols (Landsberger *et al*., 1992).

(*b*) *Biological monitoring*

Analytical methods capable of determining low concentrations of indium in biological matrices are largely lacking. The sensitivity of those methods commonly used for indium determination in geological and environmental samples, such as hydride generation atomic absorption spectrometry (Busheina & Headridge, 1982; Liao & Li, 1993), GF-AAS with preconcentration (Minamisawa *et al*., 2003), electrothermal atomization laser-excited AFS (Aucélio *et al*., 1998) and fluorimetric determination with HPLC (Uehara *et al*., 1997), is usually not sufficient for measuring indium in biological materials. Recently, indium concentrations in the body fluids of workers exposed to partially respirable particles containing unspecified indium compounds were evaluated by graphite-furnace atomic absorption spectrophotometry (Miyaki *et al*., 2003). The detection limits of indium in blood, serum and urine were found to be 0.7 µg/L, 0.4 µg/L and 0.4 µg/L, respectively. It was possible to determine indium concentrations in blood, serum and urine of the exposed workers, but those in control subjects were below the limits of detection.

Data on indium concentrations in the body fluids of occupationally non-exposed persons are insufficient to allow a reliable estimate of reference values.

1.2 Production and use

1.2.1 *Production*

Indium is recovered from fumes, dusts, slags, residues and alloys from zinc and lead–zinc smelting. The source material itself, a reduction bullion, flue dust or electrolytic slime intermediate, is leached with sulfuric or hydrochloric acid, the solutions are concentrated if necessary, and crude indium is recovered as ≥ 99% metal. This impure indium is then refined to 99.99%, 99.999%, 99.9999% or to higher grades by a variety of classical chemical and electrochemical processes (Slattery, 1995; Felix, 2003).

Indium combines with several non-metallic elements, including phosphorus, to form semiconducting compounds. Indium phosphide is prepared by direct combination of the highly-purified elements at elevated temperature and pressure under controlled conditions.

Indium phosphide is also obtained by thermal decomposition of a mixture of a trialkyl indium compound and phosphine (PH_3) (Slattery, 1995; Felix, 2003).

Single crystals of indium phosphide for the manufacture of semiconductor wafers are prepared by the liquid encapsulated Czochralski method. In this method, a single crystal is pulled through a boric oxide liquid encapsulant starting from a single crystal seed and a melt of polycrystalline indium phosphide. For specifications that require doping, the dopant (Fe, S, Sn or Zn), is added to the melt before extrusion of the single crystal. High pressure is applied inside the chamber to prevent decomposition of the indium phosphide. The single crystal is shaped into a cylinder of the appropriate diameter by grinding. The crystal is then sliced into wafers (InPACT, 2003).

World production of indium was constant at approximately 200 tonnes/year between 1995 and 1999, and rapidly increased to over 300 tonnes in 2000. Major producers of indium in 2002 and production levels (tonnes) were: China (85), France (65), Japan (60), Canada (45), Belgium (40), the Russian Federation (15), Peru (5) and other countries (20) (Jorgenson, 1997–2003, 2002; McCutcheon, 2001).

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

1.2.2 *Use*

Indium phosphide is a semiconductor and is probably the best understood semiconductor after silicon and gallium arsenide. Indium phosphide is used primarily for the fabrication of optoelectronic devices, because it is operating at high efficiency and high power. It is also used in the fabrication of laser diodes, LEDs, heterojunction bipolar transistors for optoelectronic integration, and in solar cells. Indium phosphide is also used in certain niche areas such as high-performance ICs. The use of indium phosphide in field effect transistor ICs is being driven by two application areas: microelectronics, where indium-aluminium arsenide/indium-gallium arsenide/indium phosphide-based high-electron mobility transistors are used in millimetre-wave frequencies; and optoelectronics, where indium phosphide-based field effect transistors are incorporated into long-wavelength optoelectronic components such as lasers and photodetectors in optoelectronic ICs (Materials Database, 2003; Szweda, 2003).

One of the key advantages of indium phosphide is its potential for the fabrication of very small devices. Because indium phosphide and its ternary (InGaAs) and quaternary (InGaAsP) derivatives have relatively higher refractive indices than those of other optical materials, these compounds allow for devices with much sharper and smaller bends. As their energy band gap is also closer to light energy, electro-optical effects are stronger than those in other materials (which again translates into shorter distances and lower drive voltages). As a result, extremely small devices can be produced: dice are typically < 5 mm and for many functions (e.g. lasers, modulators) they are 1 mm or less (Reade Advanced Materials, 1997; CyOptics, 2002).

Japan accounts for about 56% of the consumption of available indium phosphide wafers, and Europe and the USA for 22% each (Bliss, 2001). In 1998, it was estimated that the use of indium for semiconductor applications worldwide was 19 tonnes (McCutcheon, 2001).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Indium phosphide does not occur naturally. Indium is present in the earth's crust at concentrations of 50–200 μg/kg and is recovered primarily as a by-product of zinc smelting. Indium is also found in trace amounts in association with sulfide ores of iron, tin, lead, cobalt, bismuth and copper (Beliles, 1994; Slattery, 1995; Blazka, 1998; Slattery, 1999).

1.3.2 *Occupational exposure*

Exposure to indium phosphide occurs predominantly in the microelectronics industry where workers are involved in the production of indium phosphide crystals, ingots and wafers, in grinding and sawing operations, in device fabrication and in clean-up activities. NIOSH estimated that in 1981 approximately 180 000 workers were employed in the microelectronics industry in the USA, with over 500 plants manufacturing semiconductors (NIOSH, 1985). No assessment of occupational exposure is available specifically for indium phosphide.

In a study of workplace exposure to unspecified indium compounds at a factory in Japan (Miyaki *et al.*, 2003), concentrations of indium in blood and urine were determined for workers exposed ($n = 107$) and those not exposed ($n = 24$) to water-insoluble partially-respirable indium-containing particles in workplace air. Concentrations reported (geometric mean ± GSD) in blood were 4.09 ± 7.15 μg/L and 0.45 ± 1.73 μg/L in exposed and non-exposed workers, respectively, and in urine were 0.93 ± 4.26 μg/L and < 0.4 μg/L for exposed and non-exposed workers, respectively.

1.3.3 *Environmental exposure*

There are no data available on environmental exposure to indium phosphide.

Indium has been detected in air (43 ng/m^3), seawater (20 μg/L) and rainwater (0.59 μg/L). Indium concentrations of up to 10 μg/kg have been detected in beef and pork, and up to 15 mg/kg in algae, fish and shellfish from contaminated water near smelters. The average daily human intake of indium is estimated to be 8–10 μg/day and is regarded as minimal (Fowler, 1986; Scansetti, 1992; Blazka, 1998).

1.4 Regulations and guidelines

Occupational exposure limits have not been established specifically for indium phosphide. Table 1 presents occupational exposure limits and guidelines from several countries for indium and indium compounds in workplace air.

Table 1. Occupational exposure limits and guidelines for indium and indium compounds

Country or region	Concentration (mg/m^3) (as indium)	Interpretation[a]
Australia	0.1	TWA
Belgium	0.1	TWA
Canada		
Alberta	0.1	TWA
	0.3	STEL
Quebec	0.1	TWA
China	0.1	TWA
	0.3	STEL
Finland	0.1	TWA
Ireland	0.1	TWA
	0.3	STEL
Malaysia	0.1	TWA
Mexico	0.1	TWA
	0.3	STEL
Netherlands	0.1	TWA
New Zealand	0.1	TWA
Norway	0.1	TWA
South Africa	0.1	TWA
	0.3	STEL
Spain	0.1	TWA
Sweden	0.1	TWA
Switzerland	0.1	TWA
UK	0.1	TWA (MEL)
	0.3	STEL
USA[b]		
ACGIH	0.1	TWA (TLV)
NIOSH	0.1	TWA (REL)

From Työsuojelusäädöksiä (2002); ACGIH Worldwide® (2003); Suva (2003)

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

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

2. Studies of Cancer in Humans

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

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

In a study undertaken by the National Toxicology Program (2001), groups of 60 male and 60 female B6C3F$_1$ mice, 6 weeks of age, were exposed to particulate aerosols of indium phosphide (purity, > 99%; MMAD, 1.2 μm; GSD, 1.7–1.8 μm) at concentrations of 0, 0.03, 0.1 or 0.3 mg/m^3 for 6 h per day on 5 days per week for 22 weeks (0.1 and 0.3 mg/m^3) or 105 weeks (0 and 0.03 mg/m^3). An interim sacrifice of 10 males and 10 females per group after 3 months showed increased lung weights and lung lesions in animals exposed to 0.1 or 0.3 mg/m^3. The changes were considered sufficiently severe that exposure was discontinued in these groups and the animals were maintained on filtered air from the termination of exposure at week 22 until the end of the study. Survival rates were decreased in exposed males and females compared with chamber controls (survival rates: 37/50 (control), 24/50 (low dose), 29/50 (mid dose) or 27/50 (high dose) in males and 42/50, 13/50, 33/50 or 21/50 in females, respectively; mean survival times: 711, 660, 685 or 679 days in males and 713, 655, 712 or 654 days in females, respectively). Mean body weights were decreased in males exposed to 0.03 and 0.3 mg/m^3 and in all exposed females compared with chamber controls. Incidences of neoplasms and non-neoplastic lesions are reported in Tables 2 and 3.

There was an increased incidence of lung neoplasia in male and female mice exposed to indium phosphide. Alveolar/bronchiolar adenomas and many of the alveolar/bronchiolar carcinomas resembled those which arise spontaneously. However, exposure to indium phosphide did not cause increased incidences of neoplasms in other tissues. The lung carcinomas were distinguished from adenomas by local invasion, metastasis and/or greater anaplasia and/or pleomorphism of component cells. Some of the carcinomas differed somewhat from spontaneous carcinomas. Carcinomas in mice exposed to indium phosphide were very anaplastic with papillary and sclerosing patterns; several appeared to have spread outside the lungs into the mediastinum and some to distant metastases. A few appeared to have extensive intrapulmonary spread which in several instances was diagnosed as multiple carcinoma. Alveolar epithelial hyperplasia in the lung is generally considered to be a precursor to neoplasia in the mouse but was not significantly increased in male or female mice exposed to indium phosphide. There were increased incidences of chronic active inflammation, alveolar proteinosis and foreign bodies (indium phosphide

Table 2. Incidence of neoplasms and non-neoplastic lesions of the lung and associated lymph nodes in mice in a 2-year inhalation study of indium phosphide

Lesions observed	No. of mice exposed to indium phosphide at concentrations (mg/m^3) of			
	0 (chamber control)	0.03	0.1[a]	0.3[a]
Males				
Lung				
Total no. examined	50	50	50	50
No. with:				
Alveolar epithelium, hyperplasia	2 (1.5)[b]	5 (2.4)	3 (2.7)	7 (2.1)
Chronic active inflammation	2 (1.0)	50[c] (2.9)	45[c] (1.6)	46[c] (2.1)
Alveolus, proteinosis	0	14[c] (1.0)	0	10[c] (1.0)
Foreign body (indium phosphide particles)	0	49[c] (1.0)	42[c]	49[c]
Serosa, fibrosis	0	50[c] (3.5)	49[c] (2.0)	50[c] (2.4)
Alveolar/bronchiolar adenoma, multiple	1	2	0	3
Alveolar/bronchiolar adenoma (includes multiple)	13	9	7	13
Alveolar/bronchiolar carcinoma, multiple	1	8[d]	3	14
Alveolar/bronchiolar carcinoma (includes multiple)	6	15[c]	22[c]	13[d]
Alveolar/bronchiolar adenoma or carcinoma (includes multiple)	18	23	24	21
Pleural mesothelium, hyperplasia	0	19[c] (2.1)	4 (2.0)	6[d] (1.5)
Lymph node, bronchial				
Total no. examined	35	48	45	48
No. with:				
Hyperplasia	2 (2.5)	36[c] (2.3)	22[c] (2.0)	22[c] (2.0)
Foreign body (indium phosphide particles)	0	43[c] (1.0)	40[c] (1.0)	40[c] (1.0)
Lymph node, mediastinal				
Total no. examined	40	49	45	48
No. with:				
Hyperplasia	0	34[c] (2.5)	17[c] (2.1)	27[c] (2.2)
Foreign body (indium phosphide particles)	0	24[c] (1.0)	14[c] (1.0)	25[c] (1.0)

Table 2 (contd)

Lesions observed	No. of mice exposed to indium phosphide at concentrations (mg/m^3) of			
	0 (chamber control)	0.03	0.1[a]	0.3[a]
Females				
Lung				
Total no. examined	50	50	50	50
No. with:				
Alveolar epithelium, hyperplasia	0	1 (2.0)	1 (3.0)	2 (2.0)
Chronic active inflammation	2 (2.5)	49[c] (2.9)	45[c] (1.7)	50[c] (2.1)
Alveolus, proteinosis	0	31[c] (1.1)	0	8[c] (1.4)
Foreign body	0	49[c] (1.0)	36[c]	49[c]
Serosa, fibrosis	0	50[c] (3.8)	47[c] (1.8)	49[c] (2.5)
Alveolar/bronchiolar adenoma, multiple	0	0	1	2
Alveolar/bronchiolar adenoma (includes multiple)	3	6	10[d]	7
Alveolar/bronchiolar carcinoma, multiple	0	1	0	0
Alveolar/bronchiolar carcinoma (includes multiple)	1	6	5	7
Alveolar/bronchiolar adenoma or carcinoma (includes multiple)	4	11[d]	15[d]	14[c]
Pleural mesothelium, hyperplasia	0	16[c] (1.8)	3 (1.7)	13[c] (1.9)
Lymph node, bronchial				
Total no. examined	36	50	48	50
No. with:				
Hyperplasia	5 (1.8)	42[c] (2.8)	31[c] (2.2)	28[c] (2.2)
Foreign body (indium phosphide particles)	0	44[c] (1.0)	33[c] (1.0)	40[c] (1.0)
Lymph node, mediastinal				
Total no. examined	42	48	46	49
No. with:				
Hyperplasia	2 (2.0)	40[c] (3.0)	11[c] (2.2)	29[c] (2.6)
Foreign body	0	20[c] (1.0)	7[c] (1.0)	16[c] (1.0)

From National Toxicology Program (2001)

[a] Exposure stopped after 22 weeks.

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

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

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

Table 3. Incidence of neoplasms and non-neoplastic lesions of the liver in mice in a 2-year inhalation study of indium phosphide

Lesions observed	No. of mice exposed to indium phosphide at concentrations (mg/m^3) of			
	0 (chamber control)	0.03	0.1[a]	0.3[a]
Males				
Liver				
No. examined microscopically	50	50	50	50
Eosinophilic focus	10	16[b]	19[b]	18[b]
Hepatocellular adenoma, multiple	8	13	10	14
Hepatocellular adenoma (includes multiple)	17	24	23	32
Hepatocellular carcinoma, multiple	1	7[b]	10[c]	5
Hepatocellular carcinoma (includes multiple)	11	22[b]	23[b]	16
Hepatoblastoma				
Hepatocellular adenoma, hepatocellular	0	1	0	0
carcinomas, or hepatoblastoma (includes multiple)	26	40	37	39
Females				
Liver				
No. examined microscopically	50	50	50	50
Eosinophilic focus	6	9	4	12[b]
Hepatocellular adenoma, multiple	12	14	18	14
Hepatocellular adenoma (includes multiple)	2	4	1	2
Hepatocellular carcinoma, multiple	6	17[c]	8	10
Hepatoblastoma	0	0	0	1
Hepatocellular adenoma, hepatocellular carcinomas, or hepatoblastoma (includes multiple)	18	28[c]	24	23

From National Toxicology Program (2001)

[a] Exposure stopped after 22 weeks.

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

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

particles) in the lungs of exposed mice. A prominent feature of the inflammatory process was the presence of pleural fibrosis (serosal fibrosis). Usually, these fibrotic areas were associated with areas of inflammation. Pulmonary interstitial fibrosis was an uncommon finding in control animals. The incidence of visceral pleural mesothelial hyperplasia was increased in males and females exposed to 0.03 and 0.3 mg/m^3 indium phosphide. Usually in association with chronic inflammation and fibrosis, the pleural mesothelium from many animals was hypertrophic and/or hyperplastic. Normal visceral mesothelium is a single layer of flattened epithelium, whereas affected mesothelium ranged from a single layer of plump (hypertrophic) cells to several layers of rounded cells (hyperplasia). In the more severe cases, the proliferations formed papillary fronds that projected into the pleural cavity.

There were increased incidences of hepatocellular adenoma and carcinoma in males and females. The incidence of multiple hepatocellular tumours per animal was increased in exposed groups. The incidence of eosinophilic foci was increased in all groups of exposed males and in females exposed to 0.3 mg/m^3. Foci of hepatocellular alteration, hepatocellular adenoma, and hepatocellular carcinoma are thought to represent a spectrum that constitutes the progression of proliferative liver lesions. The increased incidence of liver lesions observed in this study was considered to be related to exposure to indium phosphide. Although there was an increased incidence of rare neoplasms of the small intestine in male mice, this was not statistically significant and it was uncertain whether these neoplasms were a result of exposure to indium phosphide (National Toxicology Program, 2001).

3.1.2 *Rat*

In a study undertaken by the National Toxicology Program (2001), groups of 60 male and 60 female Fischer 344/N rats, 6 weeks of age, were exposed to particulate aerosols of indium phosphide (purity, > 99%; MMAD, 1.2 μm; GSD, 1.7–1.8 μm) at concentrations of 0, 0.03, 0.1, or 0.3 mg/m^3 for 6 h per day on 5 days per week for 22 weeks (0.1 and 0.3 mg/m^3 groups) or 105 weeks (0 and 0.03 mg/m^3 groups). An interim sacrifice of 10 males and 10 females per group after 3 months showed increased lung weights, microcytic erythrocytosis, and lesions in the respiratory tract and lung-associated lymph nodes in animals exposed to 0.1 or 0.3 mg/m^3. These changes were considered sufficiently severe to justify discontinuing exposure after 22 weeks and these animals were maintained on filtered air from termination of exposure at week 22 until the end of the study. No adverse effects on survival were observed in treated males or females compared with chamber controls (survival rates: 27/50 (control), 29/50 (low dose), 29/50 (mid dose) or 26/50 (high dose) in males and 34/50, 31/50, 36/50 or 34/50 in females, respectively; mean survival times: 667, 695, 678 or 688 days in males and 682, 671, 697 or 686 days in females, respectively). No adverse effects on mean body weight were observed in treated males or females compared with chamber controls. Incidences of neoplasms and non-neoplastic lesions are reported in Tables 4 and 5.

Table 4. Incidence of neoplasms and non-neoplastic lesions of the lung in rats in a 2-year inhalation study of indium phosphide

Lesions observed	No. of rats exposed to indium phosphide at concentrations (mg/m^3) of			
	0 (chamber control)	0.03	0.1[a]	0.3[a]
Males				
Lung				
Total no. examined	50	50	50	50
Atypical hyperplasia	0	16[c] (3.1)[b]	23[c] (3.3)	39[c] (3.8)
Chronic active inflammation	5 (1.2)	50[c] (3.8)	50[c] (3.4)	50[c] (4.0)
Alveolar epithelium, metaplasia	0	45[c] (3.1)	45[c] (2.8)	48[c] (3.2)
Foreign body	0	50[c] (2.2)	50[c] (1.9)	50[c] (2.1)
Alveolus, proteinosis	0	50[c] (3.7)	48[c] (2.0)	47[c] (3.4)
Interstitium, fibrosis	0	49[c] (3.7)	50[c] (3.5)	50[c] (3.9)
Alveolar epithelium, hyperplasia	11 (1.5)	20 (2.4)	21[d] (2.1)	31[c] (2.6)
Squamous metaplasia	0	1 (2.0)	3 (3.0	4 (2.5)
Squamous cyst	0	1 (4.0)	3 (3.0)	2 (3.0)
Alveolar/bronchiolar adenoma, multiple	1	5	8[d]	12[c]
Alveolar/bronchiolar adenoma (includes multiple)	6	13	27[c]	30[c]
Alveolar/bronchiolar carcinoma, multiple	0	2	1	5[d]
Alveolar/bronchiolar carcinoma (includes multiple)	1	10[c]	8[d]	16[c]
Alveolar/bronchiolar adenoma or carcinoma	7/50	22/50[c]	30/50[c]	35/50[c]
Squamous cell carcinoma	0/50	0/50	0/50	4/50
Females				
Lung				
Total no. examined	50	50	50	50
Atypical hyperplasia	0	8[c] (2.8)	8[c] (2.9)	39[c] (3.8)
Chronic active inflammation	10 (1.0)	49[c] (3.0)	50[c] (2.6)	49[c] (3.9)
Alveolar epithelium, metaplasia	0	46[c] (3.3)	47[c] (2.4)	48[c] (3.8)
Foreign body	0	49[c] (2.1)	50[c] (1.8)	50[c] (2.0)
Alveolus, proteinosis	0	49[c] (3.7)	47[c] (2.0)	50[c] (3.8)
Interstitium, fibrosis	0	48[c] (2.9)	50[c] (2.6)	49[c] (3.9)
Alveolar epithelium, hyperplasia	8 (1.5)	15 (2.1)	22[c] (2.0)	16[d] (1.8)
Squamous metaplasia	0	2 (1.5)	1 (2.0)	4 (2.5)
Squamous cyst	0	1 (4.0)	1 (4.0)	10[c] (3.6)
Alveolar/bronchiolar adenoma, multiple	0	1	1	1
Alveolar/bronchiolar adenoma (includes multiple)	0	7[c]	5[d]	19[c]
Alveolar/bronchiolar carcinoma, multiple	0	1	0	7[c]

Table 4 (contd)

Lesions observed	No. of rats exposed to indium phosphide at concentrations (mg/m^3) of			
	0 (chamber control)	0.03	0.1[a]	0.3[a]
Alveolar/bronchiolar carcinoma (includes multiple)	1	3	1	11[c]
Alveolar/bronchiolar adenoma or carcinoma	1/50	10/50[c]	6/50	26/50[c]

From National Toxicology Program (2001)
[a] Exposure stopped after 22 weeks.
[b] Average severity grade of lesions in affected animals: 1, minimal; 2, mild; 3, moderate; 4, marked
[c] Significantly different ($p \leq 0.01$) from the chamber control group by the Poly-3 test
[d] Significantly different ($p \leq 0.05$) from the chamber control group by the Poly-3 test

There was an increased incidence of lung neoplasms in male and female rats exposed to indium phosphide but no increased incidence of neoplasms in other tissues was observed. Proliferative lesions of the lung included alveolar/bronchiolar neoplasms and squamous-cell carcinomas as well as alveolar epithelial hyperplasia and atypical hyperplasia of alveolar epithelium. Alveolar/bronchiolar adenomas, typical of those observed spontaneously in Fischer 344/N rats, were generally distinct masses that often compressed surrounding tissue. Alveolar/bronchiolar carcinomas had similar cellular patterns but were generally larger and had one or more of the following histological features: heterogenous growth pattern, cellular pleomorphism and/or atypia, and local invasion or metastasis. A number of exposed males and females had multiple alveolar/bronchiolar neoplasms. It was not usually possible to determine microscopically if these represented intrapulmonary metastases of a malignant neoplasm or were multiple independent neoplasms. Included in the spectrum of lesions was a proliferation of alveolar/bronchiolar epithelium with a very prominent fibrous component not typically seen in alveolar/bronchiolar tumours of rodents. The smallest lesions were usually observed adjacent to areas of chronic inflammation. Small lesions with modest amounts of peripheral epithelial proliferation were diagnosed as atypical hyperplasia, while larger lesions with florid epithelial proliferation, marked cellular pleomorphism, and/or local invasion were diagnosed as alveolar/bronchiolar adenoma or carcinoma. While squamous epithelium is not normally observed within the lung, squamous metaplasia of alveolar/bronchiolar epithelium is a relatively common response to pulmonary injury and occurred in a few rats in each exposed group. Squamous metaplasia consisted of a small cluster of alveoli in which the normal epithelium was replaced by multiple layers of flattened squamous epithelial cells that occasionally formed keratin. Cystic squamous lesions also occurred and were rimmed by a band (varying in thickness from a few to many cell layers) of viable squamous epithelium with a large central core of keratin. Squamous-cell carcinomas were observed in four males exposed to 0.3 mg/m^3 indium phosphide. These

Table 5. Incidence of neoplasms and non-neoplastic lesions of the adrenal medulla in rats in a 2-year inhalation study of indium phosphide

Lesions observed	No. of rats exposed to indium phosphide at concentrations (mg/m^3) of			
	0 (chamber control)	0.03	0.1[a]	0.3[a]
Males				
Adrenal medulla				
Number examined microscopically	50	50	49	50
Hyperplasia	26 (2.2)[b]	26 (2.4)	24 (2.4)	32 (2.3)
Benign pheochromocytoma, bilateral	0	6[c]	4	5[c]
Benign pheochromocytoma (includes bilateral)	10	22	16	23
Complex pheochromocytoma	0	1	0	0
Malignant pheochromocytoma	0	3	3	1
Benign, complex or malignant pheochromocytoma	10	26[d]	18[c]	24[d]
Females				
Adrenal medulla				
Number examined microscopically	50	48	50	40
Hyperplasia	6 (1.8)	13[c] (2.2)	9 (2.3)	15[c] (2.1)
Benign pheochromocytoma, bilateral	0	0	0	2
Benign pheochromocytoma (includes bilateral)	2	6	2	9
Malignant pheochromocytoma	0	0	0	1
Benign or malignant pheochromocytoma	2	6	2	9

From National Toxicology Program (2001)
[a] Exposure stopped after 22 weeks.
[b] Average severity grade of lesions in affected animals: 1, minimal; 2, mild; 3, moderate; 4, marked
[c] Significantly different ($p \leq 0.05$) from the chamber control group by the Poly-3 test
[d] Significantly different ($p \leq 0.01$) from the chamber control group by the Poly-3 test

neoplasms ranged from fairly well-differentiated squamous-cell carcinomas to poorly-differentiated and anaplastic ones.

There was an increased incidence of pheochromocytoma in male and female rats and an increased incidence of medullary hyperplasia in females. Focal hyperplasia and pheochromocytoma were considered to constitute a morphologic continuum in the adrenal medulla. There was also a marginal increase in neoplasms typical of those observed spontaneously in male and female Fischer 344/N rats. These included fibromas of the skin in males, mammary gland carcinomas in females, and mononuclear cell leukaemia in males and females. It was uncertain whether these neoplasms were a result of exposure to indium phosphide (National Toxicology Program, 2001).

3.1.3 *Comparison of findings from the rat and mouse inhalation studies*

The alveolar/bronchiolar adenomas found in rats exposed to indium phosphide (National Toxicology Program, 2001) closely resembled those found spontaneously in aged rats. Most alveolar/bronchiolar adenomas and carcinomas in mice exposed to indium phosphide also resembled those occurring spontaneously in $B6C3F_1$ mice (National Toxicology Program, 2001). However, some of the carcinomas were different from those occurring spontaneously in that they were very anaplastic with papillary and sclerosing patterns and often spread outside the lung into the mediastinum and distant metastases. A few appeared extensively throughout the lung and thus were diagnosed as multiple carcinomas. The neoplastic responses in the lungs of mice were even more significant than those in rats, because mice generally do not respond to particulate exposure by developing lung neoplasms, even at higher exposure concentrations.

In mice, exposure to indium phosphide also caused inflammatory and proliferative lesions of the mesothelium of the visceral and parietal pleura, another uncommon response to nonfibrous particulate exposure. Pleural fibrosis was a prominent component of the chronic inflammation and involved both visceral and parietal pleura with adhesions. Significantly, pulmonary interstitial fibrosis was uncommon in mice exposed to indium phosphide.

As a result of discontinuing exposure of the 0.1 and 0.3 mg/m^3 groups to indium phosphide at 21 or 22 weeks, only the groups receiving 0.03 mg/m^3 were exposed for 2 years. Therefore, typical concentration-related responses in neoplasms, based solely on external exposure concentration of particulate indium phosphide, were not expected. The amount of indium retained in the lung and that absorbed systemically must also be considered (see Table 6). The lung deposition and clearance model was used to estimate the total amount of indium deposited in the lungs of mice and rats after termination of exposure, the lung burdens at the end of the 2-year study, and the area under the lung-burden curves (AUC). For both species, the estimates at the end of 2 years indicated that the lung burdens in the groups exposed continuously to 0.03 mg/m^3 were greater than those of the other exposed groups (0.1 or 0.3 mg/m^3), with the lung burdens of the groups exposed to 0.1 mg/m^3 being the lowest. Because of the slow clearance of indium, the lung burdens in the groups exposed to 0.1 and 0.3 mg/m^3 were approximately 25% of the maximum levels in rats and 8% in mice, 83 to 84 weeks after exposure was stopped. The AUCs and the total amount of indium deposited per lung indicated that the groups exposed to 0.3 mg/m^3 received a greater amount of indium phosphide than the other two groups with the group exposed to 0.1 mg/m^3 being the lowest. Regardless of how the total ‘dose’ of indium to the lung was estimated, the group exposed to 0.1 mg/m^3 had less total exposure than the other two groups, implying that this group may be considered the ‘low dose’ in these studies. Therefore, lung-burden data should be considered when evaluating lung neoplasia incidence.

Table 6. Estimates of exposure of rats and mice to indium phosphide for 2 years based on a lung deposition and clearance model

Parameters of exposure	Exposure group		
	Rat/mouse	Rat[a]/mouse[b]	Rat[a]/mouse[b]
	0.03 mg/m^3	0.1 mg/m^3	0.3 mg/m^3
Lung burden at 2 years (μg In/lung)	65.1/6.2	10.2/0.5	31.9/2.3
Total amount deposited per lung (μg In/lung)	72/15	57/11	150/37
First-year AUC (μg In/lung × days of study)	6368/1001	11 502/1764	31 239/6078
Second-year AUC (μg In/lung × days of study)	18 244/2032	6275/486	18 532/1986
Total AUC (μg In/lung × days of study)	24 612/3000	17 777/2200	49 771/8000

AUC, area under the lung burden curve
From National Toxicology Program (2001)
[a] Exposure was discontinued and animals were maintained on filtered air from exposure termination at week 22 until the end of the study.
[b] Exposure was discontinued and animals were maintained on filtered air from exposure termination at week 21 until the end of the study.

3.2 Intratracheal instillation

Hamster

Tanaka and colleagues (1996) studied indium phosphide in hamsters. Groups of 30 male Syrian golden hamsters, 8 weeks of age, received intratracheal instillations of 0 or 0.5 mg phosphorus/animal indium phosphide (purity, ≥ 99.99 %; particle mean count diameter, 3.9 μm [GSD, 2.88 μm]) in phosphate buffer solution once a week for 15 weeks and were observed during their total life span (approximately 105 weeks). Survival after 15 instillations was 29/30 controls and 26/30 treated hamsters. There was no exposure-related mortality (survival time, 433 ± 170 days in exposed hamsters versus 443 ± 169 days in controls) and all exposed animals had died by 689 days (controls, 737 days). Histopathological examination of 23 exposed hamsters showed proteinosis-like lesions in 19/23, alveolar or bronchiolar cell hyperplasia in 9/23, squamous-cell metaplasia in 1/23 and particle deposition in 23/23 animals. There was no treatment-related increase in neoplasms of the lungs or other organs (liver, forestomach, pancreas or lymph nodes). [The Working Group concluded that because of the small number of animals, and because of the extent and duration of exposure by intratracheal instillation, this study may not have provided for adequate assessment of carcinogenic activity.]

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

4.1 Deposition, retention, clearance and metabolism

The absorption and distribution of indium is highly dependent on its chemical form. Indium phosphide has low solubility in synthetic simulated body fluids (Gamble solution) (Kabe *et al*., 1996).

4.1.1 *Humans*

A study (Miyaki *et al.*, 2003) of concentrations of indium in blood, serum and urine of workers exposed (n = 107) or not exposed (n = 24) to water-insoluble indium-containing particulates in workplace air is described in detail in Section 1.3.2. In each of the three biological fluids, concentrations of indium were clearly higher in exposed workers than in unexposed workers.

4.1.2 *Experimental systems*

(*a*) *Indium phosphide*

(i) *Inhalation studies in rats and mice*

The deposition and clearance of indium phosphide have been studied by the National Toxicology Program (2001). Groups of 15 male Fischer 344 rats designated for tissue burden analyses and five male rats designated for post-exposure tissue burden analyses were exposed to particulate aerosols of indium phosphide at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6 h (plus 12 min build-up time) per day on 5 days per week for 14 weeks. Indium continued to accumulate in lung tissue, blood, serum and testes throughout the exposure period. At day 5, the concentrations of indium ranged from 13 to 500 μg/g lung and concentrations of up to 1 mg/g lung were measured after exposure to 100 mg/m^3 indium phosphide for 14 weeks.

Lung clearance half-lives during exposure were in the order of 47–104 days. At 14 days after exposure, the half-life increased to about 200 days. Blood and serum indium concentrations in all exposed animals were found to be similar at the end of exposure and at 112 days after exposure. Concentrations of indium in testis tissue continued to increase more than twofold after exposure ended in rats exposed to 10- and 30-mg/m^3 concentrations of indium phosphide. Indium concentrations reached 7.20 ± 2.4 μg/g testis 14 days after the end of exposure to 100 mg/m^3.

In a further study (National Toxicology Program, 2001), groups of 60 male and 60 female rats and mice were exposed to particulate aerosols of indium phosphide at concen-

trations of 0, 0.03, 0.1, or 0.3 mg/m^3 (MMAD ~1.2 μm), for 6 h (plus 12 min build-up time) per day on 5 days per week for 22 weeks (rats) and 21 weeks (mice) (0.1 and 0.3 mg/m^3 groups) or 105 weeks (0 and 0.03 mg/m^3 groups, rats and mice). Animals in the 0.1- and 0.3-mg/m^3 groups were maintained on filtered air from exposure termination at week 22 until the end of the study. In rats, the lung indium burden at 5 months was proportional to exposure. At 12 months, 34.3 ± 1.87 μg indium per lung was measured in the male rats of the 0.03-mg/m^3 exposure group. The estimated lung clearance was long (half-life, 2422 days) and the mean indium concentration in serum at 12 months was high (3.4 ± 0.2 ng/g) in the 0.03-mg/m^3 exposure group. Results for B6C3F$_1$ mice exposed to 0.03, 0.1 or 0.3 mg/m^3 were similar although there were quantitative differences in lung burden and kinetic parameters. The mean indium concentration in the lungs at 12 months was 4.87 ± 0.65 μg per lung for male mice in the low-exposure group (0.03 mg/m^3). Lung clearance half-lives of 144 and 163 days were estimated for mice in the 0.1- and 0.3-mg/m^3 exposure groups, respectively, compared with 262 and 291 days for rats exposed to the same concentrations.

Exposure of male rats for 5 days per week for 2 years to 0.03 mg/m^3 indium phosphide resulted in a mean indium concentration of 7.65 ± 0.36 μg/g lung tissue at 5 months, i.e. a fourfold lower concentration compared with that found at 14 weeks exposure to 1 mg/m^3 indium phosphide. Lung clearance half-lives for indium phosphide in male rats in the 2-year studies were estimated to be 2422, 262 and 291 days for 0.03-, 0.1- and 0.3-mg/m^3 exposure concentrations of indium phosphide, respectively. In male B6C3F$_1$ mice exposed to 0.03 mg/m^3 for 2 years, the mean indium concentration in the lung at 5 months was 8.52 ± 1.44 ng/g lung. Indium phosphide lung clearance half-lives were 230, 144 and 163 days for male mice exposed to 0.03, 0.1 and 0.3 mg/m^3 indium phosphide, respectively (National Toxicology Program, 2001).

Deposition and clearance during long-term exposure of rats and mice to indium phosphide appeared to follow zero-order (constant rate) kinetics. The burden of indium retained in the lung throughout the experiments was proportional to exposure concentration and duration. The studies indicated that elimination of indium was quite slow. For both species, estimates at the end of 2 years indicated that the lung burdens in the groups continuously exposed to 0.03 mg/m^3 were greater than those in the groups exposed to 0.1 or 0.3 mg/m^3 where exposure was terminated at 22 weeks. Because of the slow clearance of indium, the lung burdens in the groups exposed to 0.1 and 0.3 mg/m^3, 83 weeks after exposure was stopped, were approximately 35–50% and 16–28% of the maximum concentrations in rats and mice, respectively. These findings were also compatible with the results from the 14-week study in which concentrations in testes of rats exposed to 10 and 30 mg/m^3 indium phosphide continued to increase more than twofold after exposure ended (National Toxicology Program, 2001).

(ii) *Intratracheal administration in rats*

After an intratracheal instillation into male Fischer rats of 10 mg/kg bw particulate indium phosphide (1.73 ± 0.85-μm particles), Zheng *et al.* (1994) found minimal absorp-

tion, i.e. < 0.23% urinary excretion over a 10-day period. Retention at 96 h in the body (except in lung) was 0.36%; 73% of the administered dose was recovered in faeces, probably reflecting mucociliary transport followed by ingestion.

Uemura *et al*. (1997) exposed Fischer 344 rats to 0, 1, 10 and 100 mg/kg bw particulate indium phosphide (80% of the particles were < 0.8 μm in diameter) by intratracheal instillation. Indium, determined by use of AAS was detected at concentrations of 25 ng/g and 58 ng/g in liver and spleen, respectively, 1 day after instillation of 1 mg/kg bw indium phosphide. On day 7, the concentrations were 14 and 19 ng/g in these organs. Indium concentrations in serum increased significantly from day 1 to day 7 in animals that had received the highest dose. Toxic effects were obvious in the lungs but all rats survived. In this experiment, toxicity of indium phosphide was found to be much lower than that of more soluble compounds, such as indium chloride and indium nitrate (see e.g. Zheng *et al.*, 1994).

(iii) *Intraperitoneal administration and gavage*

Kabe *et al*. (1996) studied male ICR mice after gavage and intraperitoneal injection of 0, 1000, 3000 and 5000 mg/kg bw indium phosphide suspended in 0.3 mL physiological saline and found minimal absorption after gavage with 2.4-μm particles but a dose-dependent increase in indium concentrations in serum after intraperitoneal administration. Mean indium concentrations were 1 and 4 μg/g in the liver and kidney, respectively, in mice given a single oral dose of 5000 mg/kg bw. Intraperitoneal administration resulted in accumulation of indium mainly in the lung (> 200 μg/g) and liver (about 300 μg/g) as measured by GF-AAS.

(*b*) *Other indium compounds*

(i) *Mice*

After intravenous injection of ^{113}In in mice, Stern *et al.* (1967) found that 50–60% of the injected radioactivity remained in the blood after 3 h. Castronovo and Wagner (1973) studied ^{114}In administered to mice as ionic indium chloride or as colloidal hydrated indium oxide and reported biphasic excretion patterns for both compounds, with half-life values of 1.9 and 69 days for indium chloride and 2 and 74 days for indium oxide. Ionic indium chloride concentrated primarily in the kidney while colloidal indium oxide was concentrated in the liver and reticuloendothelial system 4 days after a dose sufficient to cause the death of all animals.

(ii) *Rats*

Smith *et al*. (1960) studied the metabolism of $^{114}InCl_3$ in rats and found that more than half of the administered dose had been absorbed or excreted 4 days after intratracheal instillation, and intramuscular and subcutaneous injections. At 30 days after administration, 33–40% of the indium dose had been eliminated via faeces and urine independent of the route of administration.

Blazka *et al*. (1994) studied the distribution of indium trichloride after intratracheal instillation of 1.3 mg/kg bw in Fischer 344 rats. The rats were killed at different time-points up to 56 days after exposure and indium content of the lungs was determined. During the first 8 days after treatment, 87% of the indium was removed from the lung. Over the following 48 days less than 10% of the indium retained at 8 days was eliminated. It was concluded that indium chloride was capable of causing severe lung damage. [The Working Group noted the significant pulmonary retention for this soluble indium compound.]

4.2 Toxic effects

4.2.1 *Humans*

There are no published reports specific to the toxicity of indium phosphide in humans. A study by Raiciulescu *et al*. (1972) reported vascular shock in three of 770 patients injected with colloidal ^{113}In during liver scans.

4.2.2 *Experimental systems*

There is little information about the toxic effects in animals of indium phosphide either *in vivo* or *in vitro*. In general, the toxicity of indium compounds is dependent upon the form (solubility), the dose and the route of administration. When compared with the acute toxicity of other indium compounds, indium phosphide is less toxic (Venugopal & Luckey, 1978; National Toxicology Program, 2001).

(*a*) *Indium phosphide*

Oda (1997) investigated the toxicity of indium phosphide particles (78% < 1 μm diameter) administered by intratracheal instillation of 0, 0.2, 6.0 and 62.0 μg/kg bw in male Fischer 344 rats that were subsequently observed for 8 days. Indium was not detected in the serum, liver, kidney, spleen, thymus or brain. A dose-related increase in SOD activity was observed in BALF on day 1 in all exposed groups, with no increase in inflammatory cells or total protein. LDH activity was increased on day 1 in the group that received the highest dose. On day 8, an increase in neutrophil and lymphocyte counts, LDH activity, and total protein, phospholipid and cholesterol concentrations was observed in BALF, together with desquamation of alveolar epithelial cells and the presence of amorphous exudate in the alveolar lumen as determined by histopathological examination, but only in rats that received the highest dose (62.0 μg/kg bw).

In another experiment from the same laboratory (Uemura *et al*., 1997), male Fischer 344 rats (SPF grade) were exposed to intratracheal instillations of 0, 1, 10 or 100 mg/kg indium phosphide (mean diameter, 0.8 μm). The number of neutrophils in BALF increased considerably, in a dose-dependent manner, 1 and 7 days after indium phosphide administration. Indium phosphide particles were phagocytosed by macrophages and there was a large number of collapsed or broken macrophages at 7 days. LDH activity and the concen-

trations of total protein, total phospholipid and total cholesterol in BALF had increased in a dose-dependent manner 7 days after administration of indium phosphide. Histopathological examination of the lungs showed infiltration of macrophages and neutrophils, accompanied by broken macrophages, exfoliated alveolar cells and eosinophilic exudate. Indium phosphide particles were observed in the interstitium as well as in the lumen of the lung.

In a study conducted by the National Toxicology Program (2001) (described in Section 4.1.2), rats and mice were exposed to 0, 1, 3, 10, 30 or 100 mg/m^3 of indium phosphide by inhalation 5 days per week for 14 weeks. Examination of the lungs at the end of the exposure period revealed pulmonary inflammation characterized by alveolar proteinosis, chronic inflammation, interstitial fibrosis and alveolar epithelial hyperplasia. In addition, microcytic erythrocytosis, consistent with bone-marrow hyperplasia and haematopoietic cell proliferation of the spleen, were observed in both rats and mice. Hepatocellular necrosis was indicated by the increased activities in serum of alanine aminotransferase and sorbitol dehydrogenase in all groups of male and female rats exposed to concentrations of 10 mg/m^3 or greater. These findings were confirmed by histopathological examination of the liver in both sexes exposed to 100 mg/m^3.

In further studies (National Toxicology Program, 2001; see also Section 4.1.2), groups of 60 male and 60 female B6C3F$_1$ mice and 60 male and 60 female Fischer 344/N rats, 6 weeks of age, were exposed to particulate aerosols of indium phosphide (purity, > 99%; MMAD, 1.2 μm; GSD, 1.7–1.8 μm) at concentrations of 0, 0.03, 0.1 or 0.3 mg/m^3 for 6 h per day on 5 days per week for 22 weeks (rats) and 21 weeks (mice) (0.1 and 0.3 mg/m^3) or 105 weeks (0 and 0.03 mg/m^3). Exposure to indium phosphide caused dose-related increases in the incidence of proliferative and inflammatory lesions, especially in the lung, in both rats and mice (see Tables 2 and 3 in Section 3). In a subsequent evaluation of lung tissues collected during the 2-year National Toxicology Program study, Gottschling *et al.* (2001) used immunohistochemical techniques to show that concentrations of inducible nitric oxide synthase and cyclooxygenase-2 were elevated in inflammatory foci after 3 months of exposure to indium phosphide. In lungs of animals exposed for 2 years, inducible nitric oxide synthase, cyclooxygenase-2 and glutathione-*S*-transferase Pi were expressed and 8-OHdG was increased in non-neoplastic and neoplastic lesions. Glutathione-*S*-transferase Pi and 8-OHdG enhancement was observed in cells of carcinoma epithelium, atypical hyperplasia and squamous cysts. The results suggested that oxidative stress in pulmonary lesions may contribute to the carcinogenic process (Upham & Wagner, 2001).

(*b*) *Other indium compounds*

In a study by Tanaka *et al.* (1996), male Syrian golden hamsters received indium arsenide or indium phosphide particles by intratracheal instillation of a dose containing 0.5 mg arsenic or phosphorus once a week for 15 weeks and were observed until the animals died [for about 105 weeks]. The cumulative gain in body weight was suppressed significantly in the indium arsenide-treated hamsters and not in the indium phosphide-treated group, compared with the control animals. Histopathological examination of the lungs showed that, in the animals treated with indium phosphide or indium arsenide, the inci-

dence of proteinosis-like lesions, alveolar or bronchiolar cell hyperplasia, pneumonia, emphysema and metaplastic ossification, including infiltration of macrophages and lymphocytes into the alveolar space was significantly higher than that observed in controls. Particles of each compound were observed in the region of the alveolar septum and space as well as in the lymph nodes (Tanaka *et al*., 1996).

A number of studies (Woods *et al*., 1979; Fowler, 1986; Conner *et al*., 1995) have shown that soluble indium administered as indium chloride, or indium arsenide particles, is a potent inducer of haeme oxygenase which is the rate-limiting enzyme in the haeme degradation pathway. Induction of this enzyme is used as a molecular marker of oxidative stress and, following acute administration of indium, is associated with marked decreases in cytochrome P450 and attendant mixed function oxidase activities in the liver of rats. Alterations in the activities of these mixed function oxidases may change cellular responsiveness to a number of known organic carcinogens found in semiconductor production facilities (Woods *et al*., 1979; Fowler *et al.*, 1993).

Exposure to indium, indium arsenide and indium chloride has been shown to produce a number of effects on gene-expression patterns, including inhibition of expression of a number of stress proteins induced by arsenic (Fowler, 1986, 1988; Conner *et al*., 1993). The marked inhibitory effects of indium on protein synthesis may play a role in altering the activities of DNA repair enzymes and the expression of proteins involved in regulating apoptosis: low doses of indium chloride induced apoptosis in rat thymocytes, whereas higher doses caused necrotic cell death (Bustamante *et al*., 1997). These results provide another possible mechanism by which this element may contribute to the carcinogenic process, depending upon dose.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Six studies in experimental animals have been published; indium nitrate ($In(NO_3)_3 \cdot 4.5H_2O$) (Ferm & Carpenter, 1970) or indium trichloride ($InCl_3$) (Chapin *et al*.,1995; Nakajima *et al*., 1998, 1999, 2000) were used in five of these studies and given by oral gavage or intravenous injection. The overall results show that fetal development in rats is more affected than female or male reproductive capacity. Gross congenital malformations were observed in rat embryos. Mice were less susceptible to the teratogenicity of indium.

In the National Toxicology Program (2001) study, developmental toxicity was examined in Swiss (CD-1) mice and Sprague-Dawley rats exposed to 0, 1, 10 or 100 mg/m^3 indium phosphide by inhalation. Rats were exposed on gestation days 4–19 and mice were exposed on days 4 –17. In rats, exposure to indium phosphide by inhalation did not

induce maternal or fetal toxicity, malformations or effects on any developmental parameters. Exposure of mice to the highest dose resulted in early deaths and slightly reduced body weight gain (not statistically significant); lung weights were significantly increased in all mice exposed to indium phosphide. Renal haemorrhage was observed in some fetuses in the group exposed to 100 mg/m^3, but no significant teratogenicity or developmental effects could be attributed to exposure.

4.4 Genetic and related effects

No reports of genetic effects of indium phosphide in humans were found in the literature.

In a study carried out by the National Toxicology Program (2001) (described in detail in Section 3.1.1), no significant increases in the frequencies of micronucleated normochromatic erythrocytes were noted in the peripheral blood samples of male or female B6C3F$_1$ mice exposed by inhalation to indium phosphide in concentrations up to 30 mg/m^3 in a 14-week study. There was a significant increase in micronucleated polychromatic erythrocytes in male, but not in female mice exposed to 30 mg/m^3. The percentage of polychromatic erythrocytes was not altered in males or females (National Toxicology Program, 2001).

In the 2-year inhalation study of indium phosphide (0.03 and 0.3 mg/m^3) in male and female B6C3F$_1$ mice (National Toxicology Program, 2001), β-catenin and *H-ras* mutations were assessed in hepatocellular adenomas and carcinomas. The frequency of *H-ras* codon 61 mutations in the indium phosphide-induced hepatocellular neoplasms was similar to that observed in controls. The frequency of β-catenin mutations was concentration-dependent: in the group exposed to 0.3 mg/m^3 indium phosphide, 40% of the hepatocellular neoplasms showed β-catenin mutations compared with 10% in controls.

4.5 Mechanistic considerations

Inhalation of indium phosphide causes pulmonary inflammation associated with oxidative stress. The data of Gottschling *et al.* (2001) suggest that this inflammation may progress to atypical hyperplasia and neoplasia in the lungs in rats.

It has been suggested that induction of apoptosis *in vitro* in rat thymocytes by indium chloride at low concentrations occurs through alterations of the intracellular redox status, or of intracellular homeostasis (Bustamante *et al.*, 1997). This apoptotic effect has been shown to trigger repair-associated cell proliferation and may contribute to the risk for development of neoplasia.

Analysis of genetic alterations in indium phosphide-induced hepatocellular adenomas and carcinomas revealed mutations in H-*ras* and β-catenin that were identical to those found in human hepatocellular neoplasms (De la Coste *et al.*, 1998). This suggests a similar pathway of carcinogenesis in both species.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Indium phosphide is used in the microelectronics industry because of its photovoltaic properties. It is produced as high-purity, single crystals cut into wafers and other shapes, which are used primarily for optoelectronic devices and in integrated circuits. Exposure to indium phosphide may occur in the microelectronics industry where workers are involved in the production of indium phosphide crystals, ingots and wafers, in grinding and sawing operations and in device fabrication.

5.2 Human carcinogenicity data

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

5.3 Animal carcinogenicity data

Indium phosphide was tested for carcinogenicity in a single study in mice and rats by inhalation exposure. Exposure to indium phosphide caused an increased incidence of alveolar/bronchiolar carcinomas in male mice and alveolar/bronchiolar adenomas and carcinomas in female mice and male and female rats. There was also a significant increase in the incidence of hepatocellular adenomas/carcinomas in exposed male and female mice and an increased incidence of benign and malignant pheochromocytomas of the adrenal gland in male and female rats. Other findings, which may have been exposure-related, were marginal increases in the incidences of adenomas/carcinomas of the small intestine in male mice, mononuclear-cell leukaemia in males and female rats, fibroma of the skin in male rats and carcinoma of the mammary gland in female rats. Indium phosphide was tested by intratracheal instillation in male hamsters and showed no carcinogenic response. However, due to the study design, it was not considered for evaluation.

5.4 Other relevant data

Indium phosphide has low solubility, and uptake from the gastrointestinal tract is low. Lung toxicity has been observed in long-term inhalation studies with indium phosphide. The lung tissue burden is high and elimination from the lung is very slow. In rats, concentrations of indium phosphide in blood, serum and testes could be followed for over 100 days after cessation of exposure by inhalation. The concentration of indium in the testes continued to increase, but the testicular tissue burden remained much lower than that in the lung. In various experimental systems using different routes of administration, accumu-

lation of indium phosphide has also been demonstrated in liver, spleen and kidney. Indium is eliminated via urine and faeces.

Important toxic effects of intratracheally instilled indium phosphide particles are the induction of pulmonary inflammation, alveolar or bronchiolar hyperplasia, pneumonia and emphysema. Indium phosphide gave rise to enhanced activities of superoxide dismutase, nitric oxide synthase, cyclooxygenase and lactate dehydrogenase in bronchoalveolar lavage fluid, and to increased neutrophil and lymphocyte counts. At high doses, eosinophilic exudates and desquamation of alveolar epithelial cells were observed. Soluble indium was a potent inducer of haeme oxygenase, a marker of oxidative stress. Indium also showed inhibitory effects on protein synthesis and, at higher doses, on apoptosis.

No data were available on reproductive and developmental effects of indium phosphide in humans. Apart from slightly reduced pregnancy rates, no reproductive effects were observed in rats exposed to indium phosphide by inhalation. Mice exposed under comparable conditions were much more sensitive, showing early fetal deaths and reduced body weight gain. There is no evidence that indium phosphide is teratogenic.

Micronucleus formation was observed in male, but not in female mice exposed to indium phosphide by inhalation. No other data on genetic and related effects as a result of exposure to indium phosphide were available. An association between oxidative stress and inflammation, possibly leading to lung neoplasia has been described in rats *in vivo*. Exposure of mice to indium phosphide by inhalation for 2 years was shown to cause an increase in β-catenin somatic mutations in liver neoplasms. Indium phosphide triggers apoptosis *in vitro*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of indium phosphide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of indium phosphide.

Overall evaluation

Indium phosphide is *probably carcinogenic to humans (Group 2A)*.

In the absence of data on cancer in humans, the final evaluation for the carcinogenicity of indium phosphide was upgraded from 2B to 2A based on the following: extraordinarily high incidences of malignant neoplasms of the lung in male and female rats and mice; increased incidences of pheochromocytomas in male and female rats; and increased incidences of hepatocellular neoplasms in male and female mice. Of significance is the fact that these increased incidences of neoplasms occurred in rats and mice exposed to extremely low concentrations of indium phosphide (0.03–0.3 mg/m^3) and, even more significant, is the fact that these increased incidences occurred in mice and rats that were exposed for only 22 weeks (0.1 and 0.3 mg/m^3) and followed for 2 years.

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