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.