

Indium phosphide and other indium compounds

includes indium phosphide, indium arsenide, indium tin oxide, CIS, CIGS

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Citation for most recent IARC review

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Current evaluation

Conclusion from the previous Monograph:

Indium phosphide is *probably carcinogenic to humans (Group 2A)*. Despite a lack of evidence from human studies, the carcinogenicity was upgraded because of the “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.” These occurred at very low doses and short exposure periods.

Exposure and biomonitoring

Occupational exposure

Since the publication of Monograph 86, production of indium compounds has increased but appears limited by the low rate of refining indium as a byproduct of zinc and lead-zinc smelting (Hageluken 2006). The most well documented exposed population likely remains the semiconductor industry. Chen (2007) estimates that over 30,000 people were employed in 2007 among 350 semiconductor manufacturing firms in Taiwan. In the United States, 255,000 workers were estimated to be involved in the manufacture or application of semiconductor chips in 2004, possibly including exposure to inorganic indium compounds (http://www.sia-online.org/cs/papers_publications/press_release_detail?pressrelease.id=221). [It is unlikely that all workers in the global semiconductor industry have been exposed to indium compounds and these workers may be exposed to a variety of other Group 1 or 2 human carcinogens].

A burgeoning industry worldwide has developed in optoelectronics (e.g., light-emitting diodes and photovoltaics) and flat panel display technology, in which a variety of indium compounds [indium phosphide, indium tin oxide (ITO), indium arsenide, indium sulfide, copper indium diselenide (CIS), copper-indium-gallium-diselenide (CIGS)] are used. The use of indium in these industries has exceeded that in the semiconductor industry; (Mikolajczak 2009) reports that 80% of indium produced or reclaimed globally is used as ITO in flat panel displays. The next largest application of indium compounds is in the photovoltaic industry, either as a semiconducting material (e.g. CIS or CIGS) or as a transparent conductive top contact (e.g. ITO). (Alsema et al., 1997, Panthani et al., 2008) Many of these technologies also involve the use of indium compounds in research and development settings. For example, nanoscale ITO powder has been proposed as a transparent, conductive coating material in the production of solar panels because of its antistatic and electro-magnetic interference-shielding properties (Cho et al., 2006). Some of these technologies result in products with short useful lives (e.g., 3-5 years for liquid crystal displays); thus indium exposure may occur during disposal or recycling of the component materials (Hagelucken 2006, Li et al., 2009). Indium radioisotopes are also widely used in medical research and therapy (Fowler 2007).

Several studies have recently evaluated exposures among semiconductor and optoelectronics workers in Asia. Miyaki et al. (2003) measured indium concentrations in whole blood, serum and urine from 107 workers exposed to water-insoluble indium particles and from 24 unexposed workers. Mean exposures in whole blood, serum, and urine (respectively) were 16.8, 14.6, and 2.45 $\mu\text{g/L}$ among the exposed workers. Among the unexposed workers, most samples were below the detection limit, with a mean concentration of 0.57 $\mu\text{g/L}$ for whole blood. Serum and whole blood concentrations were highly correlated ($r=0.987$), with a beta regression coefficient very close to 1. Whole blood concentration was also significantly correlated to urine concentration and to creatinine-adjusted urine levels (better for the latter).

Whole blood and urine concentrations of indium were measured among four groups of optoelectronics workers (no specific indium compounds mentioned) in Taiwan (Liao et al., 2004), including an unexposed group of office workers. Blood and urine concentrations (respectively) averaged 0.22 $\mu\text{g/L}$ and 0.02 $\mu\text{g/L}$ among the exposed workers and 0.14 $\mu\text{g/L}$ and 0.02 $\mu\text{g/L}$ among the unexposed workers. Blood and urine indium concentrations were found to be significantly correlated (Pearson's $r=0.194$); however, the authors commented on the greater sensitivity of blood than urine as a marker of indium exposure (in contrast to gallium and arsenic, the other metals evaluated). Job title was found to be correlated with blood indium concentrations. In addition to this study, several case reports (described below) from Japan have appeared in the literature. One (Taguchi et al., 2006) estimated serum indium concentrations of 40, 99 and 127 $\mu\text{g/L}$ among three workers with interstitial pulmonary disease (and involved in wet surface grinding of ITO) among 115 workers examined.

One recent study evaluated concentrations of indium in inhalable air and urine of workers in two Taiwanese semiconductor manufacturing sites (Chen 2007). This study included 144 exposed workers [72 production workers ("operators") and 72 engineers, with no specific compounds mentioned] and 72 unexposed administrative workers. Personal air samples were collected during a shift, and spot urine samples were collected at the end of the shift. The latter were analyzed using ICP-MS [which is preferable to GF-AAS as an analytic method]. Operators and engineers were found to have similar mean inhalable air exposure concentrations (8.4 and 7.4 $\mu\text{g/m}^3$, respectively), but each group had significantly higher air

exposures than administrative workers ($2.1 \mu\text{g}/\text{m}^3$) [We note that ambient outdoor air concentrations are at least 3 orders of magnitude lower than this, per Fowler 2007]. Similar patterns were observed for indium in urine (7.0, 5.9 and $1.2 \mu\text{g}/\text{L}$, respectively). Air and urine concentrations were found to be significantly correlated. The maximum air exposure concentration was $101 \mu\text{g}/\text{m}^3$ for an operator—this was the sole exposure above the US NIOSH recommended exposure limit (REL) of $0.1 \text{ mg}/\text{m}^3$. By contrast, 71-76% of the “exposed” workers (compared to 7% of the administrative workers) had arsenic exposure levels above the NIOSH REL. The authors use USEPA risk coefficients to derive a lifetime cancer mortality risk of 10% (Chen 2007) at the mean arsenic air concentrations. The authors attribute the highest indium exposures to the manufacture of high-brightness LEDs, telecommunication laser diodes, optical storage lasers, electric devices, and solar cells (Chen 2006, 2007). [We note that urine indium concentrations in the optoelectronics workers (Liao et al., 2004) were more than 2 orders of magnitude lower than those measured among semiconductor workers (Chen 2007); however, it is unclear how representative these two studies are of their respective industries. Also, given the high potential cancer risk from arsenic exposure and the correlation of indium and arsenic exposure, independently evaluating the risk of indium through epidemiologic studies of semiconductor workers may be difficult].

Other than blood and urine measurements, there are no clear biomarkers of exposure to indium compounds. Current methods only analyze for elemental indium and cannot distinguish between specific indium compounds. Promising research has begun on analytic methods to measure indium species in environmental (air) samples (Profumo et al., 2008), which should better characterize the likely toxicity of specific indium compounds. Liao et al. (2006) found that malondialdehyde, a biomarker of lipid peroxidation, was not correlated with indium blood or urine levels among 100 workers in the optoelectronics industry.

Cancer in humans

(inadequate, Vol 86, 2006)

Since the publication of the previous monograph, several new cancer studies have been reported among semiconductor workers. Nichols and Sorahan (2005) updated cancer incidence and mortality in a cohort of 1807 UK semiconductor industry workers that was described in the previous monograph. Small numbers of cancer deaths occurred with the added follow-up. Mortality rates for all cancers combined and for lung cancer were non-significantly elevated among male workers but not among females. Significant elevations in incidence were observed for rectal cancer in men and malignant melanoma and pancreatic cancer in women.

Beall et al. (2005) evaluated cancer mortality among 126,836 workers at 3 facilities owned by a single company; two engaged in semiconductor manufacture, masking and packaging and one in storage device manufacture. Bender et al. (2007) evaluated cancer incidence among workers at two of these three facilities (excluding one semiconductor manufacture site). Overall lung cancer SMRs in this study were 0.61 (95% CI: 0.55, 0.67) among men and 0.98 (95% CI: 0.82, 1.17) among women. SMRs for the person-time associated with longer durations of employment and greater time since first employment were also not elevated. Excluding the storage device production facility reduced the lung cancer SMRs among men and slightly increased them among women, but the values were still close to 1. In the

combined group of semiconductor facilities, women in masking tasks had a higher lung cancer SMR. [The authors note that several smoking-related diseases showed SMRs below unity.] The SIR for lung cancer at the semiconductor manufacturing facility was significantly depressed overall (0.60; 95% CI: 0.51-0.70) and among the “exposed” (i.e., non-office) workers. [Nearly half the workforce was professional and likely had lower smoking rates than the general population or than the “unexposed” office workers.] Significantly elevated SMRs and SIRs were also observed for central nervous system cancer among process equipment maintenance workers at one of the semiconductor facilities and for prostate cancer among certain workers at the storage device manufacturing facility.

Clapp (2006) reported proportionate cancer mortality ratios (PCMRs) among 31,941 decedents who worked at a large U.S. computer manufacturing company. The lung cancer PCMR was significantly depressed. Overall CNS cancer PCMRs were elevated, and PCMRs of skin melanoma and cancers of kidney and pancreas were significantly elevated in male manufacturing workers. Clapp and Hoffman (2008) analyzed death data for workers at one U.S. facility involved most recently in circuit board manufacture and reported elevated PCMRs of 3.67 (95% CI: 1.19, 8.56) for malignant melanoma and 2.20 (1.01, 4.19) for lymphoma in males. A PCMR of 1.03 (95% CI: 0.71, 1.42) was observed for lung cancer in men.

In the United States, the Semiconductor Industry Association has commissioned a study of 85,000-105,000 (numbers conflict) wafer fabrication plant employees of its member companies. A feasibility study was conducted by Johns Hopkins researchers, and the retrospective cohort study is being conducted by Vanderbilt University-Ingram Cancer Center (see http://www.sia-online.org/cs/issues/occupational_health_and_safety). [The main limitation of all the studies described above is the lack of specific information on exposure to indium compounds and on the multitude of other Group 1 or 2 carcinogens to which these employees were potentially exposed. It is also unclear whether these workers had substantial exposure to indium phosphide.]

No cancer incidence or mortality studies were found that focused specifically on indium. One case of lung cancer was reported in a non-smoking ITO worker (Nogami et al., 2008). Beyond this, there is some evidence of pulmonary effects among indium workers, similar to those seen in animal studies. Several case reports in Japan have reported fatal interstitial pneumonia (attributed to ITO particles in lung) among workers producing or using ITO (Homma et al., 2003, 2005, Taguchi and Chonan 2006, Nogami et al., 2008). A more comprehensive study of pulmonary function was conducted among 108 workers from the plant in which several cases were reported (Chonan et al., 2007). Significant interstitial pulmonary changes and reduced lung function were found in 22% of the workers, and these were associated with workplace exposure to indium. In a more recent study (Hamaguchi et al., 2008), 93 exposed and 93 unexposed ITO (and other indium compounds) workers did not exhibit significant differences in prevalence of interstitial or emphysematous pulmonary changes, but significant exposure-response relations were shown between serum indium concentrations and several biomarkers (serum KL-6, SP-D, SP-A) for early interstitial pulmonary changes among the exposed workers. [We note that it is unclear to what extent these case reports and cross-sectional studies overlap].

Cancer in experimental animals

(*sufficient*, Vol 86, 2006)

An extensive inhalation study of indium phosphide in rats and mice (NTP 2001, Gotschilling et al., 2001) demonstrated clear-cut development of lung cancers in both species of rodents although some differences between genders and species were observed. These data provided the experimental animal data for sufficiency of cancer in animals in the prior IARC review. In addition, other long-term intratracheal instillation studies in hamsters using indium arsenide and indium phosphide (Yamazaki et al., 2000) have demonstrated that both indium arsenide and indium phosphide produced similar pulmonary hyperplastic lesions. Indium arsenide was observed to produce more severe lesions than indium phosphide but this finding may be related to differences in solubility between the 2 compounds (Takanaka 2004). In addition to lung lesions, Omura et al. (2000) reported similar testicular toxic effects in hamsters following a 2 year intratracheal instillation regimen of indium phosphide and indium arsenide. The degree of lesion severity was regarded as more severe for indium arsenide (See Takanaka 2004 for review). Lison et al. (2009) evaluated the lung toxicity of sintered ITO in comparison with indium oxide (In_2O_3), tin oxide (Sn_2O_3) or a mixture of indium oxide and tin oxide (MIX) in rats after a single pharyngeal instillation. They observed the formation of oxygen centered radicals and Fenton chemistry in the presence of ITO but not the other compounds in an acellular system using EPR spectrometry. They did, however, report the formation of OH^* radicals with all the compounds tested and the silica controls in the presence of H_2O_2 . Taken together these studies indicate that indium phosphide and indium arsenide have similar toxic properties and that indium-induced reactive oxygen species may play a mechanistic role in the observed carcinogenic process.

Mechanisms of carcinogenicity

The studies by Gotschilling et al. (2001) suggested that indium phosphide-induced oxidative stress may play an important role in the pulmonary carcinogenesis of indium phosphide. The prior observation of indium arsenide induced inhibition of the heme biosynthetic pathway with attendant development of increased porphyrin excretion patterns (Conner et al., 1995) suggest that this effect could also contribute to the development of oxidative stress since porphyrins are also capable of catalyzing singlet oxygen formation. This observation coupled with the ability of indium to induce apoptosis in rat thymocytes (Bustamente et al., 1997) suggest a carcinogenic mechanism related to repair-associated cell proliferation. In addition, indium arsenide has also been shown to elicit a specific stress protein response in hamster renal tubule cells following a single intratracheal instillation of InAs which was observed to be attenuated over time and associated with the development of increased proteinuria (Fowler et al., 2005). These data suggest indium-induced suppression of this important cellular mechanism for protection against oxidative stress induced proteotoxicity. The mechanism of inhibition of protein synthesis may be related to loss of ribosomes from the rough endoplasmic reticulum following indium exposure (Fowler et al., 1983). In addition, comparative studies of using male and female hamsters (Fowler et al., 2008) showed marked gender differences in the degree to which indium altered protein expression patterns in hamster renal tubule cells. These data may be useful in helping to explain observed gender differences in indium phosphide carcinogenicity in rodents (NTP 2000).

Research needs and recommendations

The previous monograph on indium considered indium phosphide alone; since then, the use of other indium compounds [indium tin oxide (ITO), CIGS, and others] has burgeoned. More than 75% of indium is now used as ITO in flat panel displays. More than 300,000 workers are employed worldwide in the semiconductor industry, and a large number of workers are also employed in manufacturing flat panel displays and optoelectronics (including photovoltaics), and in reclaiming indium from spent indium-containing materials.

Several studies of workers in the US semiconductor industry, including a large study by NIOSH of circuit board manufacturing workers and an even larger study by a semiconductor industry trade association, are currently underway. While these studies are attempting to characterize risk associated with work in specific departments or operations, they are unlikely to inform on cancer risk of indium compounds, because: 1) little indium exposure may have occurred in past circuit board manufacturing, 2) wafer fabrication workers (those most likely to have indium phosphide exposure) are typically exposed to a wide variety of other carcinogens, including arsenic, trichloroacetic acid, tetrachloroacetic acid, and more than 20 others (Cullen et al., 2001); and 3) little historical exposure monitoring information is likely available to provide estimates of exposure to indium phosphide or other potential carcinogens, which would be necessary to evaluate the contribution of indium to any observed carcinogenicity among wafer fabrication workers.

A better approach may be to conduct (if feasible) epidemiologic studies (e.g., retrospective cohort studies) of workers involved in primary (e.g., zinc smelting) or secondary refining industries. Most primary indium refining occurs in Asia although there are two large secondary refineries in the United States and several elsewhere. Studies in secondary refineries may be more informative because of the presence of cadmium in zinc smelting. Also, the focus of secondary refineries on indium production suggests that exposures to other carcinogenic substances may be lower than those to indium. Analogy exists to the Group 1 carcinogenic metals (e.g., nickel, cadmium, and beryllium), for which the most informative studies have generally been conducted among the refiners and production facilities for these metals and metal compounds (IARC Monograph 100C, Straif et al., 2009). A series of case reports has identified pulmonary effects that may be occurring in indium-exposed workers in Asia. Studies of current exposure and biomarkers of genetic damage (using the metrics described below) of these and other indium-exposed workers may be informative in identifying early precursors of cancer.

Further experimental research is needed into the mechanisms of indium compound induced toxicity and carcinogenesis with particular focus on formation of oxidative stress and inhibition protective protein synthetic mechanisms and DNA damage. Oxidative DNA damage from indium and/or arsenic exposures could be evaluated by measurement of 8-OHdG in accessible cells (e.g., nasal epithelium, buccal cells, and circulating lymphocytes) and also micronuclei micro-RNA profiling, and chromosomal aberrations.

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