

Chemical Information Profile

for

Indium Tin Oxide [CAS No. 50926-11-9]

**Supporting Nomination for Toxicological Evaluation by the
National Toxicology Program**

June 2009



NTP
National Toxicology Program
U.S. Department of Health and Human Services

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
<http://ntp.niehs.nih.gov/>

Indium Tin Oxide Nomination Summary

Chemical Name: Indium Tin Oxide

CAS RN: 50926-11-9

Formula: In₂SnO₃

Molecular Wt.: Varies with composition

[Structure not available]

Basis for Nomination: Indium tin oxide (ITO) was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization based on increasing potential for worker exposures due to its growing use in liquid crystal displays (LCDs), concern for pulmonary toxicity and carcinogenicity based on previous findings from NTP rodent toxicology studies of indium phosphide and effects observed in exposed workers, and lack of adequate toxicity data. Numerous wet chemical (aqueous or organic solvent) and thermal processes are available for producing ITO powders and thin film coatings. Commonly, indium oxide and tin oxide powders are blended together then compacted by hot or cold isostatic pressing or by sintering to make ITO sputtering targets (compressed blocks of ITO powder). ITO may be formed directly during a coating process, e.g., reactive sputtering from indium-tin alloy targets in the presence of oxygen. Its primary application is as a thin coating on glass or plastics used for touch panels (electrochromic, electroluminescent, and LCDs); plasma displays; flat panel displays (televisions, computer screens, cell phones, etc.); field emission displays; heat reflective coatings; solar panels; cathode-ray tubes; energy efficient windows; gas sensors; and photovoltaics. It is also coated on aircraft and automobile windshields for demisting and deicing. Workers engaged in finishing compacted ITO targets by wet grinding in a Japanese plant that manufactured ITO sputtering targets exhibited lung disease, the severity of which generally increased with duration of exposure and with serum indium concentrations. Two of five cases from the same Japanese plant experienced bilateral pneumothorax and at least one of these cases died. One of the five workers, diagnosed with lung fibrosis, improved upon removal to another work area. A cohort study of 108 workers from this plant reported that 23 (21%) had significant interstitial changes and 14 (13%) had emphysematous changes. Only modest lung function decrements were noted. These conditions were reported to most likely be due to inhalation of micrometer-sized ITO particles. High serum concentrations of indium in a large fraction of the workers and former workers indicated indium dissolution from ITO particles. Biomarkers of interstitial lung changes increased with increasing mean serum indium concentrations in 20 of 93 workers who were exposed to indium metal (~10%), ITO (~50%), or other insoluble indium compounds (~40%) at two ITO target manufacturing plants and two recycling plants, and in nine of 40 (22.5%) workers who had extended exposure to other insoluble indium species. Indium was suggested as the main toxicant, as well as in studies with other indium compounds such as indium oxide and indium phosphide. Alveolitis and/or other lung inflammatory responses were observed in rats given two different ITO doses by pharyngeal aspiration. Particles and proteinaceous materials were observed in the alveolar lumen but no fibrotic response was seen up to 60-days post-treatment. In a hamster subchronic study, intratracheal instillation caused significant increases in relative lung weight and slight to moderate inflammatory lung lesions. In a similar study, two of ten animals had a slight increase in the number of seminiferous tubules with disorganization or vacuolization. Body, testis, epididymis, seminal vesicle weights, and caudal sperm count were comparable to controls. ITO was cytotoxic in mouse and rat peritoneal macrophages and rat alveolar macrophages but not to rat or mouse epithelial cells. It also induced micronuclei in rats *in vivo* but not *in vitro*.

A. Chemical Information

Molecular Identification

Chemical Name: Indium Tin Oxide (ITO) (9CI)

CAS RN: 50926-11-9*

Synonyms: Tin indium oxide

Trade Names: F-ITO; Hyviz; Indium tin oxide, Vacuum Deposition Grade, 99.999%; Microsolver LIT 41A; New Pro Coat EC-L; S 100 (electrode); SUPP-HX; UFP-HX; X 101 (oxide) [Note: These were given in the Registry record; however, only SUFP-HX and UFP-HX were confirmed in a Google search (mentioned in U.S. patents).]

Hill Formula: In₂SnO₅ (usually given as In₂O₃:SnO₂ as product, Hill formula = In₂O₅Sn)

Line Formula: Not available

Smiles Notation: Not available

PubChem SID: 3764630** (PubChem, undated)

InChI: Not available

Molecular Weight: Varies with composition

Purity of Commercial Products: nanopowder is available at purities from 99 to >99.99999% at wt. % ratios (oxide weight ratio or In-Sn atomic ratios) of 90:10 (most common), 95:5, and 80:20 (AZoM.com, 2006; Degussa AG Advanced Nanomaterials, 2006; Foyol Co., Ltd., 2008; Indium Corporation, undated; Nanophase Technologies, 2008; Reade Advanced Materials, 2006; Swarts [Indium Corp. of America], 2006; Tolcin, 2008)

Additives in Commercial Products: Some nanopowders are coated with polymers to improve compatibility in coating formulations.

Impurities in Commercial Products: Total aluminum, antimony, bismuth, chromium, copper, iron, lead, magnesium, nickel, potassium, sodium, titanium, and zinc at a total concentration of ~100 ppm (Umicore, 2005)

Mammalian Metabolites: Not available

Biodegradation Products: Not available

Environmental Transformation: Not available

Physical-Chemical Properties

Physical State: Yellow, yellow-green, gray-yellow, gray, or blue solid/powder

Tin substitutes for indium in ITO crystals forming either stannous oxide (tin[II] monoxide) or stannic oxide (tin[IV] dioxide) at the doping levels commonly used (8-10%). Much of the Sn(IV) likely exists as interstitial atoms in the indium oxide cubic bixbyite lattice rather than as replacement atoms. Crystal grain size depends on processing parameters (e.g., deposition rate and substrate temperature). Typical ITO films are 1500-3500 Ångstroms thick (BizEsp, 2007; Zhou, 2005 thesis). ITO nanopowder primary particle size is ~7-75 nm. Standard- and fine-grade powder particle sizes are 0.1-15 µm with agglomerated particles ≥31 µm. ITO nanoparticles also are available as dispersions in water or organic solvents (AZoM.com, 2006; Chagnon, 2001; Degussa AG Advanced Nanomaterials, 2006; Foyol Co., Ltd., 2008; Indium Corporation, undated; Nanophase Technologies, 2008; Reade Advanced Materials, 2006; Swarts [Indium Corp. of America], 2006; Tolcin, 2008).

Specific Gravity or Density Value: 6.65-7.34 g/cm³ (Registry, 2006); 7.14 g/cm³ (AZoM.com, 2006)

Boiling Point: Sublimes at 982 °C (Swarts [Indium Corp. of America], 2006)

Melting Point: 1910 °C (Swarts [Indium Corp. of America], 2006)

Vapor Pressure: Not available

Solubility: Insoluble in water (Swarts [Indium Corp. of America], 2006) [Note: Solubility limit of Sn in In₂O₃ is <8 atomic % (Kim et al., 2006).]

Log P = Log K_{ow}: Not available

Bioconcentration Factor(s) (species): Not available

*This is the generic CAS RN; specific CAS RNs are given for specific formulations—e.g., 71243-84-0 for $\text{In}_{1.69}\text{Sn}_{0.15}\text{O}_{2.85}$, 212075-26-8 for $\text{In}_{0.01}\text{SnO}_2$, and 180090-96-4 for $\text{In}_{0.02}\text{Sn}_{0.98}\text{O}_{1.99}$.

**This is for the compound with CAS RN 71243-84-0. A PubChem compound and substance search produced no other records for other formulations (searched via chemical name and CAS RNs).

B. Exposure Potential

U.S. Annual Production

Not available for ITO; no U.S. primary production of indium

1997-2000: consumption of indium for coatings ranged from 34-39 metric tons (up from 15 metric tons in 1996); consumption for electronic components and semiconductors ranged from 9-13 metric tons (up from the 5 metric tons in 1996) ([Jorgenson and George, 2005](#)).

2001-2005: consumption of indium increased annually from 65-115 metric tons. The United States imported 79 to ~150 metric tons per year ([Carlin, 2006](#)).

2006: U.S. indium "production" was largely from upgrading imported indium (99.97-99.99%) to purities up to 99.99999%; most indium products in the United States are currently produced by Indium Corporation of America and Umicore Indium Products. U.S. import of unwrought indium and indium powder was 100 metric tons ([Tolcin, 2008](#)).

Worldwide Annual Production

- No production volumes for ITO were found. Most production of ITO targets and sputtering is done in Japan, China, and Korea. One Japanese company, Nikko Materials Co., Ltd. produces 45% of the global ITO target ([Tolcin, 2008](#)).
- Refinery production of indium was 405 and 455 metric tons in 2004 and 2005, respectively; China was the lead indium producer with an output of 200 and 250 metric tons per year, respectively ([Carlin, 2006](#)).
- More than 70% of indium produced in the world is used in flat panel displays (FPDs) but only ~30% of the ITO in the target deposits on the desired substrates during sputtering. Used targets, sputter chamber shields, and grinding sludge account for the remaining ITO. Reclaim reprocessing can recover ~ 60-65% of the indium from the non-deposited ITO ([Carlin, 2006](#); [Jorgenson and George, 2005](#)).
- Secondary production of indium from reclaim processing of ITO scrap began to exceed primary production in 2006. The minimum world indium production used in ITO increased from 595 metric tons in 2005 to 774 metric tons in 2006 ([Phipps et al., 2007](#)).
- World production of indium in 2009 is projected to be 1512 metric tons (551 metric tons primary and 961 metric tons secondary production); the projected demand is 1555 metric tons (1281 metric tons [82%] for FPDs and 274 tons for other uses) ([Phipps et al., 2007](#)).

Production Processes

- The most common method for producing ITO targets is sintering blended indium oxide and tin oxide powders (e.g., [Okabe et al., 2000 pat.](#)).
- Indium oxide and tin oxide powders must be intimately mixed. ITO powders may be used directly. Powders are compacted by cold or hot isostatic pressing, sintering, or hot pressing. After compaction, the powders are heated for many hours at ~1500 °C for homogenization and recrystallization ([BizEsp, 2007](#); [Friz and Waibel, 2003](#)).
- After compaction of the powders, the targets are surface finished by polishing, machining, or grinding ([Lo et al., 1997 pat.](#)).
- Umicore uses pressureless sintering to produce ceramic ITO sputtering targets ([Umicore, 2005](#)).
- Co-precipitation from a solution containing both indium and tin ionic compounds also can be used. An aqueous solution of inorganic salts is basified, the precipitate washed to remove ionic compounds, and the intermediate indium tin hydroxide dried then subsequently heated to convert it to ITO (e.g., [Kim et al., 2006](#)).

Nanoparticles

- Nanoscale monophasic ITO powders have been produced directly from organic salts in organic solvents (Ba et al., 2006; Lee and Choi, 2005).
- ITO nanoparticles also are produced by sol-gel process in which controlled hydrolysis of metal alkoxides in aqueous solution leads to metal oxide nanoparticles, which must be washed, dried, and calcined (Ba et al., 2006; Zhang et al., 2004).
- A nanopowder of ~37-nm particle size and said to be ITO, although it contained phases of indium oxide and tin oxide, was prepared by combustion of an emulsion containing indium nitrate and tetrabutyltin (Bickmore et al., 1999 pat.).
- ITO nanostructure can also be synthesized by the following methods (Psuja et al., 2009):
 - hydrothermal method—mixed hydrochloric acid solution of metallic indium and tin and hydrous solution of sodium hydroxide in the form of sol are hydrothermally autoclaved and then sintered in air (Xu et al., 2005; cited by Psuja et al., 2009)
 - controlled growth technique—indium chloride and tin chloride dissolved in ethanol are dropped in 25% ammonia water with β -alanine and surfactant (Al-Dahoudi et al., 2001; cited by Psuja et al., 2009)
 - preparation of indium hydroxide, which is washed, centrifuged, dried, sintered, and then mechanically mixed with tin oxide
 - modified Pechini method—nitrides, α -hydroxyl acids, and multi-hydroxide alcohols are dissolved in water; metals are complexed by acid molecules at high temperature; crystallization of compounds via a violent combustion reaction to produce oxides

Thin Films and Other Coatings

- Spray pyrolysis and sputtering from targets (preferred method) are thermal methods used to deposit thin ITO films (Gordon, 2000). Sputtering is done in a chamber at reduced pressure. In reactive sputtering from an In-Sn alloy target, oxygen is added to oxidize the metals [less popular process since pure ITO targets have become available for sputtering (BizEsp, 2007)]. For ITO thin film patterning, photoresists are typically used as masking layers. Sputtering processes include direct-current magnetron and radiofrequency sputtering (Friz and Waibel, 2003; Zhou, 2005 thesis).
- Other thermal methods include pulsed laser deposition in an ultra-high-vacuum chamber and reactive and ion-assisted sputtering (Friz and Waibel, 2003; Zhou, 2005 thesis).
- Coatings may be produced on substrates by electrospinning sol-gel prepared ITO coatings on substrates followed by thermal processing (e.g., Zhang et al., 2004).
- ITO inks are used for screen printing to give coatings with thicknesses of ~10-30 μm for LCDs, blackwall contacts, and solar-cell antireflection coatings. The post deposition crystallization temperature (≤ 600 $^{\circ}\text{C}$) is held for more than an hour (Zhou, 2005 thesis).
- Aqueous or organic solvent-based nanoscale ITO dispersions are applied to substrates by conventional coating processes such as spray, dipping, and spin coating. Formulations may include UV-cured acrylic coatings or other transparent plastics (Degussa AG Advanced Nanomaterials, 2006).

Recycling

- Spent sputtering materials, grinding sludge, and other indium-bearing wastes generated during FPD manufacture are recycled by wet chemical methods to reclaim the separate metals (acid dissolution, precipitation at different pH), which are sent back to the start of powder production (Ceramic Industry, 02-07-08; Schlott et al., 1997 pat.).
- A simpler process was patented in which ground-up target material (<250 μm powder) was returned to a compaction step using hot isostatic pressing at a temperature low enough to prevent recrystallization and retain the primary grain size (0.1-10 μm) of the original targets (Schlott et al., 1997 pat.).
- LCD panels from dismantled computers, etc., may be smashed into glass cullet and the indium recovered by acid dissolution, etc. Each 15-inch LCD display contains about 0.5 g ITO (King County Solid Waste Division, DNRP, 2008).

Uses

- Generally used as a thin coating on glass or plastics for: touch panels; electrochromic, electroluminescent, and LCDs; plasma displays; flat panel displays; field emission displays; touch or laptop computer screens; cell phones; heat reflective coatings; solar panels; cathode-ray tubes; energy efficient windows; gas sensors; and photovoltaics (AZoM.com, 2006; Gordon, 2000; Jorgenson and George, 2005).
- Coated on aircraft and automobile windshields for demisting and deicing (AZoM.com, 2006; Gordon, 2000; Jorgenson and George, 2005).
- Coated on glass for manufacture of transparent ITO electrodes, microscope slides, infrared mirrors, etc. (PGO, undated).
- Can be used as a waveguide for photonic crystals (Giessen, 2005).
- Nanopowder is used to create an ITO target, a key material used in coating an ITO thin film for use on LCDs, etc. (AZoNano, 2006).
- Applications from the environmental and life sciences journal and patent literature not mentioned in the commercial literature include:
 - photocatalyst component for pollution control and water disinfection
 - chemical sensors and biosensors (may be implantable)
 - heaters in droplet-based microfluidic devices (e.g., "lab-on-a-chip;" some may be commercial)
 - protein and DNA microarrays (e.g., for hybridization and PCR)
 - transparent cell and tissue culture platforms that allow optical monitoring of functions (no cytotoxicity)
 - electroporation (e.g., for viral gene transfection)

[See Appendix 1 for more details.]

Occupational Exposure

- Greatest potential for exposure is due to industrial use, particularly as the use of ITO in the production of LCDs increases (Homma et al., 2003, 2005).
- The primary routes of exposure are inhalation, ingestion, and eye and skin contact (Swartz [Indium Corp. of America], 2006). Workers handling powdered ITO or engaged in machining, polishing, or wet grinding of ITO targets after compaction may inhale ITO. [Workers in Japan engaged in wet grinding of targets have developed mild to severe interstitial lung disease despite respiratory protection (e.g., Homma et al., 2003, 2005).]

General Population Exposure

Foods and Beverages, Cosmetics, etc.: Not available

Ambient Environment: Not available

Environmental Occurrence

Natural Occurrence: Not known to occur naturally

U.S. Environmental Releases: Not available

Concentrations in Environmental Media: Not available

C. Regulatory Information

U.S. Regulations

ITO was on the Priority Testing List (TSCA section 8(a)) from 2001-2006. Effective June 3, 2004, it was added to the Health and Safety Data Reporting rule (TSCA section 8(d)), requiring submission of unpublished health effects studies on pharmacokinetics, genotoxicity, subchronic and chronic toxicity, and reproductive/developmental toxicity when purity of the indium compound is $\geq 90\%$ by weight of test substance (U.S. EPA, 2004). In the 56th TSCA Interagency Testing Committee (ITC) Report, data were requested on concentrations to which workers may be exposed during manufacturing and downstream uses and numbers of workers associated with manufacturing and downstream uses (U.S. EPA, 2005). It was removed from Priority Testing List in Report 58 (U.S. EPA, 2006). A history of other U.S. EPA and ITC actions may be found in Appendix 2.

Exposure Limits (Standards and Criteria): Not available for ITO

ACGIH TLV: 0.1 mg/m³ TWA (time-weighted average) for In₂O₃ (as In)

NIOSH REL: 0.1 mg/m³ TWA for In₂O₃ (as In); 2 mg/m³ TWA for SnO₂

OSHA PEL: None listed for either compound

European Union Scientific Committee Regulations

Not available

Canadian Domestic Substances List (DSL) and Non Domestic Substances List (NDSL)

ITO is not listed in the DSL or NDSL. Indium oxide [1312-43-2] and tin oxide [1332-29-2 and 18282-10-5] are both on the public portion of the DSL (published May 4, 1994) (Environment Canada, 2008).

D. Toxicological Information

General Toxicity

Data for indium oxide (In₂O₃) and tin oxide (SnO₂) are also given below. ITO may cause severe irritation and burns to the skin or eyes. It may also burn the gastrointestinal tract if ingested. Respiratory irritation is possible from inhalation; chronic exposure may cause lung damage (Swarts [Indium Corp. of America], 2006).

Human Studies: Most of the following case reports and cohort studies are from the same Japanese processing plant where ITO sputtering targets are produced for transparent conductive films used in flat panel displays. Workers were engaged in finishing compacted (press molded) and sintered ITO targets by wet surface grinding in a well ventilated area while wearing dust masks with >95% filter efficiency. Mean diameter of airborne ITO particles was 2.5 µm (0.1-11 µm). Dust may have been suspended after splashes from the wet grinding dried on surfaces (Chonan et al., 2007).

- A 27-year-old male employed from 1994-1997 as an operator of a wet surface grinder was diagnosed in 1998 with interstitial pneumonia; diagnosis was consistent with inhalation of ITO particles.
 - Liver damage (possibly not indium-induced), emaciation, and splenomegaly were observed.
 - The indium serum concentration collected one year before death was 290 µg/L compared to a mean of 0.1 µg/L reported for healthy unexposed males (n=377).
 - The patient died three years later of bilateral pneumothorax.
 - Both tin and indium were spectroscopically identified in his lungs (Homma et al., 2003).
- A 30-year-old male engineer exposed for 4 years to ITO aerosols from wet surface grinding was diagnosed with pulmonary fibrosis with cholesterol granulomas and emphysema; these were reported most likely due to inhalation of ITO.
 - Indium serum concentration was 51 µg/L compared to normal values (<0.1 µg/L).
 - Brown particles in lung tissues contained 61% indium and 4% tin compared to 74% indium and 8% tin in the target material.
 - The mean count diameter of the ITO particles sampled in the workplace (air was not specified; might have been surface wipes [deposits due to splashing]) was 10 µm.
 - The patient recovered when removed to another area in the company (Homma et al., 2005).
- Among 115 ITO workers in the same Japanese plant, three workers who had been engaged in surface grinding for 8-12 years had severely injured lungs, which was reflected in significantly elevated KL-6 (MUC-1; Krebs von den Lungen-6), a marker of diffuse interstitial lung disease. They had high serum indium concentrations and high resolution computed tomography (HRCT) revealed interstitial and/or emphysematous changes in all three workers. One worker, a nonsmoker, had severe obstructive changes by spirometry parameters and later experience bilateral pneumothorax (Taguchi and Chonan, 2006 [PMID:16886812]).
- Of 108 males at the same Japanese plant, 23 (21%) showed significant interstitial changes. Fourteen (two nonsmokers) (13%) had emphysematous changes.
 - Elevated serum KL-6 was found in 40 of the workers.

lung damage and fibrosis in rats, while inhalation caused inflammatory changes in rat lungs (Blazka et al., 1994a [PMID:8005375], 1994b [PMID:7925195]).

Reproductive/Developmental Toxicity: Oral exposure of male Swiss mice to indium trichloride (≤ 250 mg/kg) did not affect the reproductive system. In female mice, no changes were observed in the ability to become pregnant, but fetal development was affected (i.e., increase in intrauterine deaths) (Chapin et al., 1995 [PMID:7589924]). A significant increase in fetal mortality and malformations (mainly in the tail and rib) were reported in Wistar rats given indium chloride (300 mg/kg) by i.v. injection (0.4 mg In/kg) on day 9 of pregnancy (fetuses were examined on day 20). Results from orally treated rats also were higher compared to controls but they were not statistically significant (Nakajima et al., 1998 abstr., 1998 [PMID:9876012]). In a separate experiment in which indium trichloride was administered i.v. on gestation day 10, caudal hypoplasia (e.g., apoptosis in tailbud) was observed in embryos on day 11. Similar results also were reported for 10 day old rat embryos treated *in vitro* (Nakajima et al., 2008 [PMID:18547785]). Bone and cartilage malformations were observed in 21 day old fetuses from Sprague-Dawley rats given a single i.v. injection of indium trichloride on gestation day 10 (Nakajima et al., 2007 [PMID:17646080]). In a comparative species study, mice and rats were observed to be susceptible to the embryotoxicity of indium at similar developmental stages but mice were less susceptible to the teratogenicity of indium based on gross malformation (Nakajima et al., 2000 [PMID:10910472]). The embryotoxic and teratogenic effects of indium trichloride also have been observed in rabbits (Ungváry et al., 2000 [PMID:10681097]).

Other Biological Effects: Daily oral administration of indium trichloride to Sprague-Dawley rats (200 mg/kg) on gestation days 6-15 produced hemodynamic effects. The cardiac index was increased, while cardiac output to kidneys, ovaries, uterus, and placenta was decreased (brain, lungs, and liver unaffected). Furthermore, the placenta had decreased blood flow and increased vascular resistance. The results, in combination with maternal survival over fetal mortality in the presence of noradrenaline, indicated the hemodynamic changes to be harmful to the fetus (Morvai et al., 2001 [PMID:11261901]). Dose dependent apoptosis and necrosis also were induced in rat thymocytes (Bustamante et al., 1997 [PMID:9129167]). In hamsters, it inhibited erythrocyte δ -aminolevulinic acid dehydratase (ALAD) activity. No significant changes occurred in hepatic ALAD activity, but renal ALAD was statistically decreased (Conner et al., 1995 [PMID:7538452]).

Brief summaries of the toxicological data for two other indium compounds, indium phosphide and indium arsenide, both of which are pulmonary and testicular toxicants, are given below. Physical and chemical characteristics contributing to different toxicity (potency) of various indium compounds are not well understood.

Indium Phosphide (InP) [CAS No. 22398-80-7; PubChem CID:31170 (PubChem, undated)] is used in the semiconductor industry. Absorption from the gastrointestinal tract was minimal following oral treatment of mice and rats. At 5000 mg/kg i.p. or oral, indium was detected primarily in the liver and lungs of mice. In oral studies of InP in rats, most was excreted in the feces; urinary elimination half-time was ~ 321 hours. Following i.t. instillation of InP, indium was mostly found in the lungs (HSDB, 2005c). InP given to male and female B6C3F₁ mice and F344/N rats via inhalation for three weeks produced gray to black discoloration and enlargement of the lungs; inflammatory and proliferative lesions in the lungs consisting of alveolar proteinosis, chronic inflammation, interstitial fibrosis, and alveolar epithelial hyperplasia; inflammation of the larynx; hyperplasia of the bronchial and mediastinal lymph nodes; and microcytic erythrocytosis in both species. InP particles were observed throughout the respiratory tract and in lymph nodes. The retained lung burdens of indium were proportional to exposure dose and duration, and elimination was slow. In a two-year inhalation study in mice and rats, InP was carcinogenic. An increase in the incidence of benign and malignant neoplasms of the lungs was seen in both sexes of both species. An increased incidence of liver neoplasms was also seen in male and female mice, while marginal increases in the incidences of small intestine neoplasms were seen in males only. In rats, an increased incidence of pheochromocytomas of the adrenal gland was also reported in males and

females; marginal increases were seen in the incidences of mononuclear cell leukemia in males and females, fibroma of the skin in males, and carcinoma of the mammary gland in females. InP was negative in the micronucleus test using murine erythrocytes (NTP, 2001). It was a testicular toxicant in hamsters; it decreased reproductive organ weight and caudal sperm count and induced severe histopathologic changes in the testes (Omura et al., 2000). It also induced slight to severe inflammatory lesions in the lungs (e.g., diffuse alveolar cell hyperplasia) of hamsters; effects were more severe compared to animals given ITO [see above] (Tanaka et al., 2002).

Indium Arsenide (InAs) [CAS No. 1303-11-3; PubChem CID:91500 (PubChem, undated)] is also used in the semiconductor industry. The oral LD₅₀ is >15,000 mg/kg in mice (HSDB, 2002). The subcutaneous LD₅₀ is 32,500 mg/kg in mice (ChemIDplus, undated). In hamsters, i.t. instillation of >99.9999% pure InAs, mean particle diameter 1.58 µm, produced proteinosis-like lesions or localized hyperplastic lesions (e.g., alveolar/bronchiolar cell hyperplasia with squamous cell metaplasia or squamous cell hyperplasia with keratinization), squamous cyst, inflammation, and interstitial fibrosis in the lungs (Tanaka et al., 2003). Like InP, InAs is a testicular toxicant but induces greater damage than InP (Omura et al., 2000).

Isomers: Not available

Congeners: Not available

Reactive Moieties: Indium oxide [See toxicity data above.]

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Acknowledgements

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Search Strategy

On May 8, 2006, the Registry file on STN International was searched. In the file, 198 indium tin oxides with different ratios of the constituent elements were registered. Most of these, including the one registered as 71243-84-0, had only one record in Chemical Abstracts and no records in other STN databases except MEDLINE. That number was used erroneously instead of 50926-11-9 in the 51st Report of the Toxic Substances Control Act (TSCA) Interagency Testing Committee (ITC) and carried over into the ensuing U.S. EPA rule promulgated in 2001 (the only citation for 71243-84-0 in CAPLUS). The TSCA ITC had used the correct CAS number in the 47th Report and published a correction in the 52nd Report in 2003. Various trade names in the Registry record for 50926-11-9 were not confirmed in Internet searches via the Google search engine and were omitted from the search strategy.

Files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIODBASE, BIOTECHNO, IPA, BIOSIS, and TOXCENTER were searched simultaneously on May 9, 2006, for indium tin oxide (ITO). [Note that CANCERLIT and NIOSHTIC, files once routinely included in searches, are no longer available on STN]. Reviews were sought for components indium sesquioxide and stannic oxide. [Reviews for the latter compounds were retrieved from HSDB and by searches at <http://www.inchem.org>, which includes documents published by the World Health Organization, and searches at the Agency for Toxic Substances and Disease Registry (ATSDR) website (<http://www.atsdr.cdc.gov/toxpro2.html>) for toxicology profiles.] The 708 titles from the ITO answer set L20 were examined, but only 57 records were selected to be printed in full. These were retrieved in the following groups: health-related (6), substrate for biological studies (23), other uses (19), processing (7), and not immediately classifiable (2). Records on the common applications listed in the trade literature were usually not retrieved. The applications records that were retrieved were examined for the potential of human exposure (e.g., implants) and possible contact of ITO with cultured cells and tissues and with DNA, enzymes, and other proteins.

In 2006, production information was sought at the U.S. EPA Inventory Update Rule (IUR) site and at the U.S. Geological Survey website (<http://www.usgs.gov>). Google and the Google Scholar search engines were used to clarify the use of indium tin oxide (or tin-doped indium oxide) for a number of applications

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including cell culture, water treatment, biochips/microfluidics, and glucose monitors/sensors and other biosensors after examination of the STN results.

Searches for combinations of three atoms from the same elemental groups as indium (aluminum, gallium, thallium); tin (silicon and germanium but not lead); and oxygen (sulfur, selenium, and tellurium) did not find structural analogs of interest. Internet searches for other elements with "tin oxide" or "doped indium sesquioxide" (or oxide) (Google search, Google Scholar, and PubMed) were more fruitful. Compounds of possible interest as structural analogs found by the latter approach were antimony tin oxide (Sb is a Group V element, not Group III) and indium sesquioxide doped with silicon, germanium, gallium, and cadmium. (Other elements used for doping indium sesquioxide include Cr, Er, F, Au, Ir, Li, Mn, Mo [most Google hits], Ag, Ti, and Zn.). Other tin-doped oxides [("tin doped" AND oxide) NOT indium] of some interest would be titania, silica, cadmium oxide, and zinc oxide. No toxicity studies were found for any of these in PubMed.

The history of the May 9, 2006, STN International session is reproduced below.

```
L1          34 S 71243-84-0
              SET DUPORDER FILE
L2          31 DUP REM L1 (3 DUPLICATES REMOVED)
L3          295 S 50926-11-9
L4          286 DUP REM L3 (9 DUPLICATES REMOVED)
L5          950 S INDIUM(W)(TIN OR STANNIC)(W)OXIDE
L6          14 S F(W)ITO
L7          7 DUP REM L6 (7 DUPLICATES REMOVED)
L8          7 S L7 NOT FLUORINE
L9          7 S L8 NOT L4
L10         7 SORT L7 1-7 TI
L11        1020 S L3 OR L5
L12         33 S TIN(W)DOPED(W)INDIUM(W)(OXIDE OR TRIOXIDE OR SESQUIOXIDE)
L13         5 S TIN(W)INDIUM(W)OXIDE
L14         38 S L12 OR L13
L15         78 S IN2O3(4A)SNO2
L16         32 S L14 NOT L11
L17         69 S L15 NOT L11
L18        1121 S L11 OR L14 OR L15
L19         708 DUP REM L18 (413 DUPLICATES REMOVED)
L20         708 SORT L19 1-708 TI
              SAVE L20 X0370BIOMED/A
L21        4649 S (STANNIC OR TIN)(W)OXIDE OR 18282-10-5
L22         3 S STANNIC(W)(ANHYDRIDE OR DIOXIDE)
L23         84 S TIN(W)(IV)(W)OXIDE
L24         814 S TIN(W)(PEROXIDE OR DIOXIDE)
L25        4773 S L21 OR L22 OR L23 OR L24
L26        3762 S L25 NOT L18
L27         2 S L26 AND REVIEW/DT
L28         0 S METAL(6A)OXIDE? AND REVIEW/DT AND (TIN OR STANNIC OR INDIUM)
L29         19 S OXIDE? AND REVIEW/DT AND (TIN OR STANNIC OR INDIUM)
L30         15 DUP REM L29 (4 DUPLICATES REMOVED)
L31         15 SORT L30 1-15 TI
L32        615 S INDIUM(W)(OXIDE OR TRIOXIDE OR SESQUIOXIDE)
L33         477 S 1312-43-2
L34         661 S L32 OR L33
L35         414 S L34 NOT (L18 OR L25)
L36         1 S L35 AND REVIEW/DT
L37         57 S (L26 OR L35)AND REVIEW?
L38         56 S L37 NOT REVIEW/DT
L39         48 DUP REM L38 (8 DUPLICATES REMOVED)
L40         16 S L39 AND (2000-2006)/PY
L41         16 DUP REM L40 (0 DUPLICATES REMOVED)
L42         16 SORT L41 1-16 TI
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L43 32 S L39 NOT L40
L44 32 SORT L43 1-32 TI

2008 Update: The same search strategy for ITO was repeated on STN International in a simultaneous search of the above-named files plus FSTA, FROSTI, PASCAL, and NTIS on July 8, 2008, with publications limited to 2006-2008. The titles of 425 database records were examined. Publications for indium oxide, tin oxide, or both plus the word doping or doped in this time period were limited to those that were reviews or those that contained "?toxic?," "inhal?," "pneumo?," "pulmonary," or "lung OR lungs." These limitations resulted in 53 records after duplicate removal. Examination of the titles indicated that most of the retrievals discussed information already covered in the dossier. Only 45 records were selected for printing (MEDLINE, 25; EMBASE, 4; TOXCENTER, 13; PASCAL, 1; and BIOSIS, 2). The printed records contained eight pairs of duplicates. Another 17 were removed from further consideration, often because they were about uses already covered in the dossier (a complete list of reasons for removal is available). The final selections of 20 new records (MEDLINE, 11; TOXCENTER, 7; EMBASE, 2) included four on lung disease in ITO workers, three on lung disease in tin workers, seven on processing and exposure potential, and six on uses with exposure potential.

In July 2008, additional Internet searches were done using Google and Google Scholar to find references to help clarify the discussion on ITO technology and to find particle sizes available in commercial ITO products. While searching for "indium tin oxide" AND "inhalation OR lungs OR pulmonary," a 2007 TSCA test submission that is not in the TSCATS database was found: [Laloy et al. \(2007\)](#). Subsequent check of TSCATS found no other TSCA test submissions. In August, searches regarding regulations pertinent to ITO in the United States, European Union, and Canada were conducted using various Internet sites, including Regulations.gov, GPO Access, Health Canada's The Substances List, and OECD's eChemPortal.

2009 Update: STN International database files MEDLINE, AGRICOLA, CABA, IPA, BIOSIS, TOXCENTER, FSTA, FROSTI, EMBASE, ESBIODBASE, BIOTECHNO, and NTIS were searched simultaneously on April 14, 2009, updating earlier searches.

```
L1                    0 S 71243-84-8
L2                    717 S 71243-84-0 OR 50926-11-9
L3                    2000 S INDIUM(W)(TIN OR STANNIC)(W)OXIDE
L4                    78 S TIN(W)DOPED(W)INDIUM(W)(OXIDE OR TRIOXIDE OR SESQUIOXIDE)
L5                    0 S IN203(4A)SNO2
L6                    2202 S L2 OR L3 OR L4
                      SET DUPORDER FILE
L7                    454 S L6 AND (2008-2009)/PY
L8                    338 DUP REM L7 (116 DUPLICATES REMOVED)
L9                    338 SORT L8 1-338 TI
                      SAVE L9 X3702009UP/A

L10                   6437 S (STANNIC OR TIN)(W)(OXIDE OR DIOXIDE)
L11                   112 S TIN(W)IV(W)(OXIDE OR DIOXIDE)
L12                   1 S TIN(W)PEROXIDE
L13                   6494 S L10 OR L11 OR L12
L14                   12 S L13 AND REVIEW/DT
L15                   101 S OXIDE? AND REVIEW/DT AND (TIN OR STANNIC OR INDIUM)
L16                   969 S INDIUM(W)(OXIDE OR TRIOXIDE OR SESQUIOXIDE) OR 1312-43-2
L17                   101 S (L15 OR L16) AND REVIEW/DT
L18                   1 S 18282-10-5 AND REVIEW/DT
L19                   12 S L14 OR L18
L20                   1124 S INDIUM(W)(CHLORIDE OR TRICHLORIDE) OR 10025-82-8
L21                   16 S L20 AND REVIEW/DT
L22                   116 S L17 OR L19 OR L21
L23                   106 DUP REM L22 (10 DUPLICATES REMOVED)
L24                   105 S L23 NOT L8
L25                   105 SORT L24 1-105 TI
                      SAVE L25 X3700THER09/A
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Appendix 1. Life Science Applications

Indium tin oxide applications in environmental and life sciences found in the patent and experimental literature include the following:

- Component of sensors to detect inorganic or organic chemicals in media such as atmospheric emissions, breath, and food (e.g., Lewis, 2000 pat.).
- Photocatalyst component for degrading water pollutants and disinfecting water (e.g., Eggins et al., 1999) and a conductive paint electrode to electrochemically inactivate marine bacteria (Lim et al., 2003 [PMID:12474252]).
- ITO microelectrode arrays in molecular biosensors with immobilized proteins (e.g., membrane proteins, antibodies, enzymes), nucleic acids/nucleotides, and even networks of excitable cells and microorganisms (e.g., Pancrazio et al., 1999 [PMID:10625143]; Tang et al., 2006 [PMID:16448043]). In similar applications, ITO films were used as heaters for DNA PCR in a micro total analytical system that included pumps and valves (Fukuba et al., 2003) and ITO microelectrodes were used in biosensors for DNA hybridization (e.g., Armistead and Thorp, 2000 [PMID:10959961]). ITO has been studied in the development of glucose biosensors, which may be miniaturized and implantable (e.g., Beach et al., 2005).
- Numerous studies of cultured cells and tissues on ITO-coated glass or ITO electrodes as cell-culture platforms (CCPs) take advantage of the transparency of ITO, its lack of adverse effects, and better cell adhesion and growth than achieved on conventional cell culture plastic (e.g., Tomai et al., 2000 [PMID:11065276]). Systems in which electrical field stimulation is accompanied by optically monitoring a physiological response are amenable to high-throughput screening (Burnett et al., 2004 pat.). ITO microelectrode arrays in which murine spinal cord tissue was grown were used to trigger tissue network responses for up to eight months in warm saline before electrode breakdown via oxidation and loss of light transmittance (Gross et al., 1993 [PMID:8107494]).
- ITO conductive growth surfaces were used to permit introduction of nonpermeant molecules (e.g., antibodies and genes) into adherent mammalian cells by electroporation (e.g., Raptis and Firth, 1990 [PMID:2271121]; Yamauchi et al., 2005 [PMID:16114943]).
- Patterns of ITO microelectrodes are used in digital droplet-based microfluidics biochips to induce surface tension imbalances that move nanoliter volumes of liquid droplets along the line of electrodes. Such microsystems are called lab-on-a-chip and bio-MEMs (microfluidic electromechanical devices), which automate highly repetitive laboratory tasks involving micro- and nanoscale amounts of fluids. Such biochips (which may use other methods to move the fluids) are being manufactured for commercial use (Chakrabarty and Su, 2005).
- Possible uses that would involve direct human exposure include implanted or worn biosensors, bio-MEMs (perhaps for drug delivery), and other biomedical devices with ITO microelectrodes. For example, ITO incorporation in contact lenses might allow for monitoring glucose or oxygen in tears (Mitsubayashi et al., 2001). In biocompatibility studies for materials to be chronically implanted as microelectrodes, ITO showed the least protein adsorption, a requirement for "electrode recording sites." Such electrodes might be useful for neural stimulation of movement for paralyzed individuals or for amputee prosthetics (Selvakumaran et al., 2002).

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Appendix 2. History of U.S. EPA and ITC Actions on Indium Tin Oxide

CAS No. 050926119

Chemical Indium tin oxide

Category Indium Chemicals

Action Recommended **Report 47** **Date** 11/30/2000

Notice [66FR17767](#) **FR Date** 04/03/2001

Rationale In view of the fact that indium phosphide causes tumors in rats and mice and that indium chemicals are increasingly used in the semiconductor and other industries, existing exposure limits may be inadequate to protect workers. [Indium chemicals were added to the Priority Testing List.] ([ITC Reports](#) [select Chemicals and enter CAS No.]

PAIR (Preliminary Assessment Information Reporting) rule: 7/26/01 [66FR38955](#)

HaSDR (Health and Safety Data Reporting) rule: 5/4/04 [69FR24517](#)

Action: Removed from Priority Testing List in Report 58 7/11/06 [71FR39188](#)