

# **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/>

## Data Availability Checklist for Indium Tin Oxide [50926-11-9]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat

Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L	ENDPOINT	H	M	R	L
<b>ADME</b>					<b>Developmental Toxicity</b>				
Absorption			X		Developmental abnormalities				
Distribution	X				Embryonic/fetal effects				
Metabolism					Newborn effects				
Excretion					<b>Carcinogenicity</b>				
<b>Acute Toxicity (up to 1 week)</b>					Dermal				
Dermal					Inhalation				
Inhalation*			X		Oral				
Injection					<b>Anticarcinogenicity</b>				
Ocular					Anticarcinogenic effects				
Oral					<b>Genotoxicity</b>				
<b>Subchronic Toxicity (1 to &lt;26 weeks)</b>					Cytogenetic effects			X	
Dermal					Microbial gene mutation				
Inhalation**					Gene mutation <i>in vitro</i>				
Injection					Gene mutation <i>in vivo</i>				
Oral					Germ cell effects				
<b>Chronic Toxicity (≥26 weeks)</b>					<b>Neurotoxicity</b>				
Dermal					Behavioral activity				
Inhalation*	X				Motor activity				
Injection					<b>Immunotoxicity</b>				
Oral					Immunotoxic effects			X	
<b>Synergism/Antagonism</b>					<b>Cardiovascular Toxicity</b>				
Synergistic effects					Cardiovascular effects				
Antagonistic effects					<b>Mechanistic Data</b>				
<b>Cytotoxicity</b>					Target Organs/Tissues**	X			
Cytotoxic effects		X	X		Endocrine modulation				
<b>Reproductive Toxicity</b>					Effect on enzymes				
Fertility effects					Modes of action				
Maternal effects					Effect on metabolic pathways				
Paternal effects					<b>Structure-Activity Relationships**</b>	X	X	X	X

\*Rats: pharyngeal aspiration. \*\*Data available for Syrian golden hamsters via intratracheal instillation.

The above table provides an overview of the data summarized in this profile. From left to right, column 1 and 6 list the endpoints and columns 2-5 and 7-10 identify the four species (human, rat, mouse, and rabbit) that were considered. An "X" is entered in each box that corresponds to an endpoint and species for which data are included in the profile. Blank cells indicate that no data were available in the literature.

## Indium Tin Oxide Nomination Summary

**Chemical Name:** Indium Tin Oxide

**CAS RN:** 50926-11-9

**Formula:** In<sub>2</sub>SnO<sub>3</sub>

**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

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### *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:** In<sub>2</sub>SnO<sub>3</sub> (usually given as In<sub>2</sub>O<sub>3</sub>:SnO<sub>2</sub> as product, Hill formula = In<sub>2</sub>O<sub>5</sub>Sn)

**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/cm<sup>3</sup> (Registry, 2006); 7.14 g/cm<sup>3</sup> (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 In<sub>2</sub>O<sub>3</sub> is <8 atomic % (Kim et al., 2006).]

**Log P = Log K<sub>ow</sub>:** 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**

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### ***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  $\beta$ -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,  $\alpha$ -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  $\mu\text{m}$  for LCDs, blackwall contacts, and solar-cell antireflection coatings. The post deposition crystallization temperature ( $\leq 600$   $^{\circ}\text{C}$ ) 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  $\mu\text{m}$  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  $\mu\text{m}$ ) 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**

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### *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 56<sup>th</sup> 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/m<sup>3</sup> TWA (time-weighted average) for In<sub>2</sub>O<sub>3</sub> (as In)

**NIOSH REL:** 0.1 mg/m<sup>3</sup> TWA for In<sub>2</sub>O<sub>3</sub> (as In); 2 mg/m<sup>3</sup> TWA for SnO<sub>2</sub>

**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**

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### **General Toxicity**

Data for indium oxide (In<sub>2</sub>O<sub>3</sub>) and tin oxide (SnO<sub>2</sub>) 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.



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- Although serum indium concentration and KL-6 concentration were not significantly different in surface grinders vs. those in other work rooms, the prevalence of interstitial changes and emphysematous changes in the two groups were 40% vs. 14% and 27% vs. 8%, respectively. Most workers were rotated to different operations, which may have obscured exposure differences among them.
- Of the 108 workers, the 78 who were currently exposed had serum indium concentrations of  $7.8 \pm 4.3$   $\mu\text{g/L}$ . Serum concentrations of 27 formerly employed employees were  $8.3 \pm 4.4$   $\mu\text{g/L}$ , and concentrations in nonexposed employees (38) were  $0.3 \pm 2.6$   $\mu\text{g/L}$ .
- The range of serum indium concentrations increased with increasing years of exposure and increasing interstitial changes score while the mean age of the workers in each of the quartiles was 33-34 years.
- The first quartile (mean 2.1 years of experience) had serum concentrations in the range 0.2-2.9  $\mu\text{g/L}$  and an interstitial changes score of zero.
- In the second and third quartiles (2.9 and 4.1 mean years of experience), serum indium concentrations were 3.2-8.0 and 8.3-21.7  $\mu\text{g/L}$  and the number of interstitial changes were 0-10 (score 0.5-1.0).
- In the fourth quartile (9.9 mean years of experience), the serum indium concentrations were 22.2-126.8  $\mu\text{g/L}$  and the number of interstitial changes were 0-14.5 (score 3.0).
- Modest lung function decrements were noted in those workers with interstitial changes.
- Recent efforts to reduce exposure included semi-closure of open systems such as wet surface grinding and stricter enforcement of dust respirator use (Chonan et al., 2007).
- Workers were studied from two ITO manufacturing plants and two ITO recycling plants (total 93 workers, 93 nonexposed workers) where the major indium species in the dusts to which the workers were exposed were ITO (>50%),  $\text{In}_2\text{O}_3$  or  $\text{In}(\text{OH})_3$  (~40%), and indium metal (~10%). All of these species are difficultly water soluble. Dusts were said to consist "largely of respirable-sized particles."
  - No differences were observed in lung effects between those who had inhaled mainly ITO and those who had inhaled tin-free indium compounds.
  - Although no differences were observed between exposed and nonexposed workers in parameters of spirometry or in prevalence of interstitial changes, dose-effect and dose-response relations were very clear when the workers were grouped by serum indium concentration ranges.
  - The prevalence of interstitial and emphysematous changes as well as several biochemical indicators of lung damage, especially KL-6, generally increased with increasing blood serum indium concentrations.
  - The group with the greatest changes had a mean serum concentration of 80.4  $\mu\text{g/L}$ .
  - Significant changes in KL-6 were observed in groups with mean serum concentrations between 24.2 and 80.4  $\mu\text{g/L}$  (20 workers).
  - The overall serum geometric mean of exposed workers was 8.25  $\mu\text{g/L}$  (maximum 116.9  $\mu\text{g/L}$ ) compared to 0.25  $\mu\text{g/L}$  in unexposed workers (Hamaguchi et al., 2008).

Other studies of biological monitoring of workers exposed to water-insoluble indium compounds are included for comparison.

- In a study of Japanese indium plant workers that does not clearly state in its abstract whether exposure was to ITO, no findings of interstitial lung changes were noted in the 40 workers upon HRCT examination; but serum KL-6 concentrations were elevated (>500 U/mL) in nine men (22.5%) who had significantly longer indium exposure, higher serum indium concentrations, and higher surfactant protein D (SP-D) concentrations, which were indicative of interstitial changes in the lungs (Nogami et al., 2008 [PMID:18260313]).
- Arithmetic mean values for indium in whole blood, serum, and urine of 107 Japanese workers exposed to partially respirable particles of water-insoluble indium compounds for a mean duration 4.56 years were 16.8, 14.6, and 2.45  $\mu\text{g/L}$ , respectively. Values at the 90<sup>th</sup> percentile

were 42.7, 36.1, and 6.88 µg/L, respectively. The mean blood indium concentrations in 24 unexposed workers were 0.57 µg/L (0.98 µg/L at the 90<sup>th</sup> percentile) (Miyaki et al., 2003). [The serum value 14.6 µg/L falls within the range of the workers with mean exposure duration of 4.1 years reported by Chonan et al. (2007).]

- Taiwanese optoelectronics workers (103) had mean whole blood concentrations of 0.22 µg/L [reported as ppb] compared to 0.14 µg/L in blood of 67 referents (unexposed office workers). There was little difference among the three groups of optoelectronic workers (15 in equipment maintenance, 52 dopants and thin film workers, and 36 fabrication supervisors and engineers). The mean concentrations of indium in urine were not significantly different from that of the controls (0.02-0.03 µg/L). The workers were also exposed to gallium, arsenic, and antimony. Although gallium and arsenic concentrations in the urine were significantly correlated with malondialdehyde plasma concentrations, a marker of lipid peroxidation, no such correlation for indium in urine was observed (Liao et al., 2004 [PMID:15354058], 2006 [PMID:16902371]).
- Personal air samplers worn by production workers, engineers, and office administrators (72 workers/group) at two semiconductor manufacturing plants in the Science-Based Industrial Park in Hsinchu City, Taiwan, collected inhalable air samples indicating mean (range) airborne indium concentrations of 8.4 (0.14-100.62), 7.38 (0.25-99.3), and 2.08 (0.12-17.66) µg In/m<sup>3</sup>, respectively. Urine concentrations for the three groups were 6.98 (3.05-35.89), 5.88 (3.02-34.09), and 1.24 (0.05-7.27) µg In/L, respectively. All but one of the 216 indium inhalation exposure concentrations were less than the NIOSH REL for indium and indium compounds (100 µg/m<sup>3</sup>) (NIOSH, 2005). (Exposures at this plant were probably to water-insoluble gallium arsenide and indium arsenide. Arsenic posed the greatest risk for the production workers and engineers since arsenic exposures frequently exceeded the exposure limit) (Chen et al., 2007a,b).

**Animal Studies:** Not available

**Indium Oxide:** Although extensive toxicity testing of hydrated indium (III) oxide [In(OH)<sub>3</sub>] has been done its comparability to indium oxide is questionable therefore results from studies using In(OH)<sub>3</sub> are not included here.

**Human Studies:** Not available

**Animal Studies:** Necrotizing pneumonia was reported in rats and rabbits injected intravenously (i.v.) with indium oxide. Toxic effects in rats dosed intratracheally (i.t.) included pneumonia and early fibrosis in the lungs, hyperplasia in lung lymph nodes, dystrophic changes in liver and kidneys, and inflammatory changes in the heart. Lung inflammatory changes and growth depression were observed in rats that inhaled indium oxide for three months. It was nontoxic in rats when ingested (Smith et al., 1978).

### Tin Oxide

**Human Studies:** Workers exposed to tin oxide (stannic oxide) in dusts or fumes for at least three years while engaged in metal casting (tin foundries), scrap metal recycling, or tin plating accumulated tin in their lungs without any effect on lung function, reports of fibrosis, "clinically significant emphysema," or adverse effect on mortality. One case control study in Belgium reported an odds ratio of 3.72 for risk of chronic kidney failure for persons occupationally exposed to tin, but no distinction was made as to the tin speciation (IPCS, 2005; Monteiles, 2005). Tin oxide is generally regarded as an agent that produces nonfibrotic pneumoconiosis, a benign disease with insignificant pulmonary effects. Recently, interstitial lung disease has been reported in Turkish tinsmiths who recoat tin-covered copper kitchen utensils. Turkish tanners (24), who had worked at the occupation for a mean of 41.4 years, had a high incidence (46%) of diffuse parenchymal lung diseases that appeared to be attributable to combined exposure to sulfuric acid (in a preliminary step followed by rinsing) and powdered ammonium chloride (used to pretreat the copper surface) as well as to tin oxide vapors while applying the tin, either by rubbing a pure tin bar or by sprinkling small balls of granulated tin on the hot copper surface. Two-thirds of the workers had a history of potential exposure to environmental asbestos, but asbestosis was ruled out; and 75% smoked

tobacco. High resolution computed tomography results were consistent with "respiratory bronchiolitis interstitial lung disease" in nine workers, a "usual interstitial pneumonia" in one worker, and a "non-specific interstitial pneumonia" in another (Dikensoy et al., 2008). Another study of 26 tinsmiths from the same Turkish province reported that 11 exhibited aortic valve sclerosis and left ventricle diastolic dysfunction. One of the workers had been seen before and determined to have a reversible toxic myocarditis due to tin [oxide] fumes exposure. The signs vanished after the worker refrained from exposure for six months (Gunay et al., 2006 [PMID:16326401]).

**Animal Studies:** Rats given a 50-mg dose of tin smelter dust i.t. showed dust accumulation in the lungs without connective tissue changes one year post exposure. Toxic effects observed in short-term experiments with rats exposed to tin salts were not observed in rats dosed with tin oxide (Monteiles, 2005).

### *Chemical Disposition, Metabolism, and Toxicokinetics*

**Absorption and Clearance:** Not available

**Human Studies:** High concentrations of indium in sera of workers exposed by inhalation to ITO indicated indium dissolution from ITO particles; indium appeared to be distributed to several organs (e.g., liver and spleen) via blood, which authors noted may lead to chronic adverse health effects. Two former ITO workers in Japan had serum indium concentrations of 51 and 290  $\mu\text{g/L}$  three to four years after leaving the factory compared to a mean concentration of 0.1  $\mu\text{g/L}$  reported for 377 unexposed workers (Chonan et al., 2007; Homma et al., 2003, 2005).

**Animal Studies:** Two-phase elimination of ITO from female Wistar rat lungs was observed after a single pharyngeal aspiration of ITO particles (2 or 20 mg/rat). [See acute animal studies for particle characterization.] By 15 days post-exposure, ~60% of the 2 mg and ~40% of the 20 mg dose were eliminated. Little more was cleared at the subsequent observation points up to 60 days. No blood, tissue, or urine concentrations were reported (Laloy et al., 2007).

### Indium Oxide

**Absorption and Clearance:** Minor absorption of indium was observed when rats were exposed to indium oxide via inhalation, i.t. instillation, or ingestion. More indium was absorbed in the lungs and tracheobronchial lymph nodes than in the gastrointestinal tract, likely due to the longer retention time when indium oxide is deposited in the lungs. After inhalation, lung clearance was slow. Twelve weeks after a three-month inhalation exposure to indium oxide (mean concentration of 64  $\mu\text{g/m}^3$ ), 58% of the indium oxide still in the lungs at the end of the exposure had been removed from the lungs and 69% from the tracheobronchial lymph nodes. The biological half life was calculated as 2.5 months in the lung and 1.75 months in the tracheobronchial lymph nodes. After nose-only exposure of rats to nanoparticulate (64 nm) indium oxide for one hour (~2.5  $\text{mg/m}^3$ ) 40% was deposited in the lower respiratory tract and 60% was in the nasopharyngeal region. Wide distribution to organs (greatest in the kidneys and liver) indicated "small but significant absorption," particularly during the first 24 hours of exposure. The half-life for clearance after this short exposure was 8 to 10 days. Fresh tissues from rats that were fed a diet with 8% indium oxide for three months contained ppm levels of indium (Morrow et al., 1957; Smith et al., 1978).

**Human Studies:** Not available

**Animal Studies:** When rats inhaled indium oxide (average concentration 64  $\text{mg/m}^3$ ) for two weeks, indium oxide mobilized significantly to tracheobronchial lymph nodes, but little absorption and distribution was observed. Indium concentrations in  $\mu\text{g/g}$  after two weeks (concentrations after 12 weeks are in parentheses) were 490 (10,000) in lungs, 250 (1,300) in tracheobronchial lymph nodes, 1.8 (9.2) in kidney, 0.33 (3.1) in liver, 0.25 (16) in spleen, and 0 (3.4) in bone. Tissue concentrations were higher at 24 weeks post exposure, but still represented only 10% of the lung burden with exclusion of the tracheobronchial lymph nodes. Kidneys, spleen, liver, and bone contained  $\leq 2$   $\mu\text{g In/g}$  after consuming a diet with 8% indium oxide for three months. When rats

were given indium oxide i.v. at 30 mg/kg bw, the principal deposits were in lung, liver, and spleen (Smith et al., 1978).

### Tin Oxide

**Absorption and Clearance:** The International Commission on Radiological Protection (ICRP) developed a human model for absorption of inhaled tin oxide and other compounds categorized as Type M (i.e., ~70% of the tin deposited in the alveolar interstitial regions is transferred to blood, and ~10% of the tin deposited in the bronchi and bronchiole regions and 5% of the tin deposited in the gastrointestinal tract are rapidly absorbed) (IPCS, 2005). Ingested tin is poorly absorbed, even from soluble compounds. Tin compounds ingested by rats were excreted in the feces in amounts greater than 90 to 99% of the original low dose (within 48 hours in one experiment). When given parenterally, most was excreted in the urine with a limited amount excreted in the bile. The biological half-life for inorganic tin in rat femur was calculated at 34 to 40 days and in mouse whole body, approximately 30 days (JECFA, 1982).

**Human Studies:** Long-term exposure (3 to 5 years) to tin oxide in dust and fumes from some extraction and treatment procedures of tin ores and concentrates, especially bagging of concentrates, and from certain smelting operations, caused stannosis (loading of tin in the lungs), a mild pneumoconiosis. Small dense shadows were apparent in lung X-rays. Autopsy of a worker who had no symptoms for 18 years after his last exposure revealed black pigmentation in pleura, lung parenchyma, and lymph nodes. The nodes near the bifurcation of the bronchi and bronchioles showed the heaviest pigmentation (HSDB, 2005a).

**Animal Studies:** Rats given tin oxide (1-4 i.v. doses of 250 to 1000 mg/kg bw) and observed for up to 26 months for long-term retention, showed phagocytosis and storage of tin in mononuclear cells of the reticuloendothelial system, especially the spleen, liver, bone marrow, and some lymph nodes, but no fibrosis or neoplasia was seen. Retention was also noted at some injection sites. The same disposition pattern was observed in New Zealand white rabbits given tin oxide (1-5 i.v. doses of 250 mg/kg bw) over a 6- to 26-month survival period (Fischer and Zimmerman, 1969; JECFA, 1982).

### **Acute Exposures**

In a recent rat study (TSCA test submission) the toxic effects of well characterized ITO particles (90:10 In-Sn ratio) produced by Umicore (the sponsor) were compared to those induced by indium trioxide, stannic oxide, or a mixture of the two. ITO impurities included 300 ppm zirconium, 100 ppm silicon, and <100 ppm each lead and antimony. The mass median diameter of 75% of the particles was <20  $\mu\text{m}$ , with 58% <10  $\mu\text{m}$  and 41% <20  $\mu\text{m}$ .

Route:	pharyngeal aspiration [inhaled from its placement on base of fully extended tongue]
Species:	rats
Dose/Duration:	2 or 20 mg (~1.5 or 15 mg In)/single dose
Observation Time:	$\leq$ 60 days
Effects:	lung inflammatory response indicated by increase in lactate dehydrogenase (LDH) activity 3 days after ITO treatment; increased total protein and total cells in bronchoalveolar lavage fluid in ITO-treated rats ( $> \text{In}_2\text{O}_3 > \text{mixture of In}_2\text{O}_3 + \text{SnO}_2 > \text{SnO}_2$ ). ITO produced a stronger dose-response at 15 days; higher dose induced alveolitis (thickening of the alveolar wall by 3 days with nodules around particle aggregates). Fibrotic response, as measured by lung hydroxyproline and collagen, was not induced by ITO or the other indium and tin materials within observation period. ITO-reported effects included alveolitis; increase in macrophages, lymphocytes, and polymorphonucleated neutrophils; perivascular inflammatory infiltrates; and the presence of particles and proteinaceous material in the alveolar lumen (histological response to the other indium and tin materials)

## Chemical Information Profile for Indium Tin Oxide

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at 60 days was not reported). A slight but significant increase in tumor necrosis factor-alpha was seen only in rats treated with the higher ITO dose.

Source(s): [Laloy et al. \(2007\)](#) [TSCA test submission from Umicore]; Lison et al. (2009 [PMID:19176593])

### Indium Oxide

LC<sub>50</sub>/LD<sub>50</sub> Values: i.p. LD<sub>50</sub> = 396 mg In/kg bw [mice] (Smith et al., 1978)

Route: oral (intra-gastric)  
Species: mice  
Dose/Duration: 10 g/kg bw (8270 mg In/kg bw)  
Observation Time: not provided  
Effects: 23% or 45% mortality [conflicting reports from same author]  
Source(s): Smith et al. (1978)

Route: i.v.  
Species: rats  
Dose/Duration: up to 175 mg/kg bw  
Observation Time: not provided  
Effects: extensive necrotizing pneumonia and lung edema at doses as low as 30 mg/kg bw (25 mg In/kg bw); respiratory difficulties followed by convulsions, which are common when relative large amounts of insoluble dust are i.v. injected at doses  $\geq 90$  mg/kg bw  
Source(s): Smith et al. (1978)

Route: i.v.  
Species: rabbits  
Dose/Duration: 35-68 mg/kg bw  
Observation Time: not provided  
Effects: reduced food intake; weight loss; extensive pneumonia and abnormally heavy lungs on necropsy  
Source(s): Smith et al. (1978)

Results from an animal study using a single i.t. instillation dose are included because of the long-term retention of indium oxide in the lower respiratory tract.

Route: i.t.  
Species: rats  
Dose/Duration: 50 mg (41.4 mg In)  
Observation Time: 8 months  
Effects: 36% mortality and depressed growth in 70% of surviving animals; granular dystrophy of liver and kidney cells; cloudy swelling of myocardium fibers with focal lymphoid-histiocyte infiltration in the stroma; large dust accumulation, weak fibrosis of the stroma, and hyperplasia of the lung lymphoid follicles; dust deposits, focal desquamative pneumonia, meso- and peribronchitis, alveolar membrane proliferation, and beginning fibrosis of the interstitial tissue of lungs  
Source(s): Smith et al. (1978)

### Tin Oxide

LC<sub>50</sub>/LD<sub>50</sub> Values: oral LD<sub>50</sub> > 20,000 mg/kg bw [mice and rats] ([RTECS, 2008](#))  
i.p. LD<sub>50</sub> > 6600 mg/kg bw [mice and rats] ([RTECS, 2008](#))



## Chemical Information Profile for Indium Tin Oxide

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Route: i.t.  
Species: rats  
Dose/Duration: 50 mg deposited  
Observation Time: 1 year  
Effects: dust accumulation in lungs (unaccompanied by fibrosis)  
Source(s): [Monteiles \(2005\)](#)

### ***Subchronic Exposures***

Route: i.t.  
Species: Syrian golden hamsters, male  
Dose/Duration: 6.0 mg/kg (4.5 mg In/kg) 1x/wk for 16 wk  
Observation Time: not provided  
Effects: no significant difference in body weight gain compared to controls; significant increase in relative lung weight (2.6 times) compared to controls; slight to moderate inflammatory lesions in lungs—*slight* cholesterol cleft and fibrotic proliferation; *mild* inflammatory cell infiltration, thickening of alveolar wall and pleura, and alveolar cell hyperplasia; and *moderate* exudation and accumulation of alveolar macrophages with expanded cytoplasm with or without ITO particles, necrotic cell debris, and few neutrophils within alveolar septae, alveolar spaces, or bronchiolar lumens  
Notes: ITO particles, purity >99.99%, contained 74.4% (wt%) indium and 7.8% tin. Mean count diameter of the particles was 0.95  $\mu\text{m}$ .  
Source(s): [Tanaka et al. \(2002\)](#)

### Indium Oxide

Route: oral  
Species: rats  
Dose/Duration: 8% indium oxide (6.6% In) in diet for 3 months  
Observation Time: not provided  
Effects: increased weight and food consumption; no histological changes or clinical signs of toxicity attributable to indium oxide  
Source(s): [Smith et al. \(1978\)](#)

Route: inhalation (submicron-sized particles in a chamber)  
Species: rats  
Dose/Duration: 64 mg/m<sup>3</sup> for 4 hour/day for 3 months  
Observation Time: 24 weeks post-exposure  
Effects: significant growth depression in males (especially in month 1, averaged 90 g below weight of the controls); increased lung weight; pulmonary inflammatory reactions (alveolar phagocytes or alveolar epithelial cells on membrane walls); enlarged tracheobronchial lymph nodes; 2- to 3-fold increase in absolute neutrophil count in blood  
Source(s): [Smith et al. \(1978\)](#)

Route: inhalation  
Species: rats  
Dose/Duration: 24-97 mg/m<sup>3</sup> for 224 hours  
Observation Time: up to 12 weeks post-exposure  
Effects: widespread alveolar edema; fluid was microscopically granular and contained few alveolar phagocytes, polymorphonuclear cells, and nuclear debris; alveolar walls altered with spindle-shaped and other type cells; little change in lesion

## Chemical Information Profile for Indium Tin Oxide

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during and after exposure; no fibrosis from healing process; concluded that effect on alveolar stasis resembling alveolar proteinosis in which alveolar clearance is reduced  
Source(s): HSDB (2002)

### Tin Oxide

Route: oral  
Species: rats  
Dose/Duration: ≤1% in diet, 7 days/week for 4 weeks  
Observation Time: not provided  
Effects: no adverse effects on body weight or to cardiovascular, hematopoietic, hepatic, or renal systems  
Source(s): [ATSDR \(1992\)](#); [IPCS \(2005\)](#)

### ***Chronic Exposures***

Not available

### ***Synergistic/Antagonistic Effects***

Not available for ITO

Indium Oxide: Not available

Tin Oxide: Suppressed the fibrogenic effect of silica dusts on rat lungs *in vivo* (Wang et al., 1994 [PMID:7946006])

### ***Cytotoxicity***

The responses of rat (RLE) and mouse (LA-4) epithelial cells to ITO, indium trioxide, and tin oxide showed insignificant toxicity, while silica at 200 µg/mL induced a significant increase in LDH activity after a 24-hour exposure. Both ITO and silica particles induced significant increases in mouse and rat peritoneal macrophages at 50 and 100 µg/mL. Significant increases in LDH were induced in rat alveolar macrophages by ITO and all of the other test articles except tin oxide. The response to ITO was dose-dependent and similar in intensity to that induced by silica ([Laloy et al., 2007](#); Lison et al., 2009 [PMID:19176593]).

Indium Oxide: See above.

Tin Oxide: Weak to no toxic effects in rabbit alveolar macrophages *in vitro* and *in vivo* (Labeledzka et al., 1989 [PMID:2538328]; Wang, 1988); not cytotoxic in 3T3 fibroblasts (Rushe et al., 2005 [PMID:15744616]). See also ITO discussion above.

### ***Reproductive and Developmental Toxicity***

**Human Studies:** Not available for ITO

**Animal Studies:** In male Syrian golden hamsters i.t. instilled with ITO (6.0 mg/kg bw 1x/wk for 16 wk), body weight, testis, epididymis, and seminal vesicle weights, and caudal sperm count were comparable to those of controls. Two of 10 animals had a slight increase in the number of seminiferous tubules displaying disorganization or vacuolization; a significant increase in incidence of tubules with vacuolization was observed in the epithelium (14.6% versus 7.2% for controls) ([Omura et al, 2002](#)). [Note: Water-soluble indium trichloride has been reported to induce developmental abnormalities in rats via oral or i.v. exposure (e.g., Nakajima et al., 2007 [PMID:17646080]; Ungváry et al., 2001 [PMID:11261900]). However, indium concentrations measured in serum of ITO workers (e.g., [Homma et al., 2003](#)) were much lower than those expected in rats given one-time doses of indium trichloride. See Structure-Activity Relationships below.]

Indium Oxide: Not available

Tin Oxide: Not available

### ***Carcinogenicity***

Not available

### ***Anticarcinogenicity***

Not available



### **Genetic Toxicity**

ITO increased micronuclei frequency in type II pneumocytes recovered from rats 3 days after a second administration of 2 mg (inflammatory dose) but not in RLE cells *in vitro* treated with 50-200 µg/mL. Suggests genotoxic response is related to reactive oxygen species products from inflammatory cells (Lison et al., 2009 [PMID:19176593])

Indium Oxide: Not available

Tin Oxide: Negative in the Rec assay with *Bacillus subtilis* (ATSDR, 1992)

### **Neurotoxicity**

Not available

### **Immunotoxicity**

Not available for ITO

Indium Oxide: Not available

Tin Oxide: Weak to no toxic effects in rabbit alveolar macrophages *in vitro* and *in vivo* (Labeledzka et al., 1989 [PMID:2538328]; Wang, 1988)

## **E. Mechanistic Data**

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### **Target Organs/Tissues**

**Human**: Lungs, liver, and spleen (Homma et al., 2003, 2005)

**Animal**: Lungs [hamsters] (Tanaka et al., 2002)

### **Endocrine Modulation**

Not available

### **Effect on Enzymes**

Not available

### **Modes of Action**

Not available

### **Structure-Activity Relationships**

The results from ADME studies of indium trichloride administered by various routes (i.v., i.p., i.t., and oral) and toxicological data reported from studies in laboratory animals are given below. Most of the data were from studies of embryotoxic and teratogenic effects.

Indium Trichloride [CAS No. 10025-82-8; PubChem CID:24812 (undated)] is used in electroplating and its radioisotopes are used in the treatment of tumors and in organ scanning.

**ADME**: After i.v. administered, indium trichloride was mainly excreted in the urine; when given i.p., it accumulated in the liver, passed into the small intestine, then was excreted in the feces (HSDB, 2005b). Oral exposure of male Swiss mice to indium trichloride ( $\leq 250$  mg/kg) did not affect the liver but urinary *N*-acetyl glucosaminidase in the kidney decreased (Chapin et al., 1995 [PMID:7589924]). In patients treated i.v. with  $^{111}$ indium chloride 24 or 48 hours before orchidectomy, uptake into the testes was observed. The radionuclide also was found in the seminiferous tubules (Nettleton et al., 2004). The biological half-life of  $^{114}$ indium trichloride in mice treated by i.v. injection was 1.9 days during the fast phase of removal and 69 days for the slow phase (HSDB, 2005b). In rats administered  $^{114}$ indium trichloride by i.p. injection on four consecutive days then sacrificed one hour after the last injection, indium accumulated primarily in the liver, spleen, and kidney. The highest concentrations were reported in the cytosolic fraction followed by the mitochondria from tissue homogenates. Indium observed in the serum accounted for 90% of the total activity in whole blood and it was exclusively bound to transferrin (Van Hulle et al., 2001 [PMID:11253025]).

**Toxicity**: Mouse i.p. LD<sub>50</sub>: 9500 µg/kg bw; rat i.p. and i.v. LD<sub>50</sub> values: 2370 and 4460 µg/kg bw, respectively. A single i.v. injection caused severe necrosis of the renal proximal tubules in both mice and rats, while a single i.p. injection induced an increase in smooth endoplasmic reticulum in the tubule cells (HSDB, 2005b). Intratracheal administration of indium trichloride caused severe

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 ( $\leq 250$  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  $\delta$ -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  $\sim 321$  hours. Following i.t. instillation of InP, indium was mostly found in the lungs (HSDB, 2005c). InP given to male and female B6C3F<sub>1</sub> 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 LD<sub>50</sub> is >15,000 mg/kg in mice (HSDB, 2002). The subcutaneous LD<sub>50</sub> 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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### **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 51<sup>st</sup> 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 47<sup>th</sup> Report and published a correction in the 52<sup>nd</sup> 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.

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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 X3700THERO9/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](#)