Chemical Information Profile

for

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

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

June 2009

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
ADME					**Developmental Toxicity**				
Absorption			X		Developmental abnormalities				
Distribution	X				Embryonic/fetal effects				
Metabolism					Newborn effects				
Excretion					**Carcinogenicity**				
Acute Toxicity (up to 1 week)					Dermal				
Dermal					Inhalation				
Inhalation*			X		Oral				
Injection					**Anticarcinogenicity**				
Ocular					Anticarcinogenic effects				
Oral					**Genotoxicity**				
Subchronic Toxicity (1 to <26 weeks)					Cytogenetic effects	X			
Dermal					Microbial gene mutation				
Inhalation**					Gene mutation *in vitro*				
Injection					Gene mutation *in vivo*				
Oral					Germ cell effects				
Chronic Toxicity (≥26 weeks)					**Neurotoxicity**				
Dermal					Behavioral activity				
Inhalation*	X				Motor activity				
Injection					**Immunotoxicity**				
Oral					Immunotoxic effects			X	
Synergism/Antagonism					**Cardiovascular Toxicity**				
Synergistic effects					Cardiovascular effects				
Antagonistic effects					**Mechanistic Data**				
Cytotoxicity					Target Organs/Tissues**	X			
Cytotoxic effects		X	X		Endocrine modulation				
Reproductive Toxicity					Effect on enzymes				
Fertility effects					Modes of action				
Maternal effects					Effect on metabolic pathways				
Paternal effects					**Structure-Activity Relationships****	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.Sn.O **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: In.Sn.O (usually given as In_2O_3:SnO_2 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/cm^3 (Registry, 2006); 7.14 g/cm^3 (AZoM.com, 2006)
Boiling Point: Sublimes at 982 ºC (Swarts [Indium Corp. of America], 2006)
Melting Point: 1910 ºC (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_2O_3 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 $In_{1.69}$ $Sn_{0.15}O_{2.85}$, 212075-26-8 for $In_{0.01}SnO_2$, and 180090-96-4 for $In_{0.02}Sn_{0.98}O_{1.99}$.
**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 ºC 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 ºC) 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 (Swarts [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 ≥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/m^3 TWA (time-weighted average) for In_2O_3 (as In)
NIOSH REL: 0. 1 mg/m^3 TWA for In_2O_3 (as In); 2 mg/m^3 TWA for SnO_2
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 (In_2O_3) and tin oxide (SnO_2) 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.

  - 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 ± 4.3 µg/L. Serum concentrations of 27 formerly employed employees were 8.3 ± 4.4 µg/L, and concentrations in nonexposed employees (38) were 0.3 ± 2.6 µg/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 µg/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 µg/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 µg/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%), In_2O_3 or $In(OH)_3$ (~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 µg/L.
  - Significant changes in KL-6 were observed in groups with mean serum concentrations between 24.2 and 80.4 µg/L (20 workers).
  - The overall serum geometric mean of exposed workers was 8.25 µg/L (maximum 116.9 µg/L) compared to 0.25 µg/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 µg/L, respectively. Values at the 90th 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 90th 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^3, 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^3) (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 [$In(OH)_3$] has been done its comparability to indium oxide is questionable therefore results from studies using $In(OH)_3$ 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 tinners (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 µg/L three to four years after leaving the factory compared to a mean concentration of 0.1 µg/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 µg/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 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 mg/m^3) for two weeks, indium oxide mobilized significantly to tracheobronchial lymph nodes, but little absorption and distribution was observed. Indium concentrations in µg/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 ≤2 µg 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 µm, with 58% <10 µm and 41% <20 µm.

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:	≤ 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 (> In_2O_3 > mixture of In_2O_3 + SnO_2 > 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

	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_{50}/LD_{50} Values:	i.p. LD_{50} = 396 mg In/kg bw [mice] (Smith et al., 1978)
Route:	oral (intragastric)
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 ≥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_{50}/LD_{50} Values:	oral LD_{50} > 20,000 mg/kg bw [mice and rats] (RTECS, 2008) i.p. LD_{50} > 6600 mg/kg bw [mice and rats] (RTECS, 2008)

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 µm.
Source(s):	Tanaka et al. (2002)

<u>Indium Oxide</u>

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^3 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^3 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

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* (Labedzka 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* (Labedzka et al., 1989 [PMID:2538328]; Wang, 1988)

E. Mechanistic Data

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 (≤ 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_{50}: 9500 µg/kg bw; rat i.p. and i.v. LD_{50} 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 (≤ 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 B6C3F_1 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_{50} is >15,000 mg/kg in mice (HSDB, 2002). The subcutaneous LD_{50} 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.]

References

Al-Dahoudi, N., Bisht, H., Gobbert, C., Krajewski, T., and Aegerter, M. A. 2001. Transparent conducting, anti-static and anti-static-anti-glare coatings on plastic substrates. Thin Solid Films 392:299-304. Cited by Psuja et al. (2009)

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Chapter 3. Health Effects. In: Toxicological Profile for Tin and Tin Compounds. Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services, Atlanta, GA. Internet address: http://www.atsdr.cdc.gov/toxprofiles/tp55-c3.pdf. Last accessed on August 18, 2008.

AZoM.com. (The A to Z of Materials). 2006. Indium tin oxide (ITO) – properties and applications. Internet address: http://www.azom.com/details.asp?ArticleID=2349. Copyright 2000-2008. Last accessed on August 19, 2008.

AZoNano (The A to Z of Nanotechnology). 2006. Samsung Corning complete indium tin oxide (ITO) nanopowder manufacturing facility. Internet address: http://www.azonano.com/details.asp?ArticleID=1020. Posted October 9, 2002. Copyright 2000-2006. Last accessed on August 19, 2008.

Ba, J., Rohlfing, D.F., Feldhoff, A., Brezesinski, T., Djerdj, I., Wark, M., and Niederberger, M. 2006. Nonaqueous synthesis of uniform indium tin oxide nanocrystals and their electrical conductivity in dependence of the tin oxide concentration. Chem Mater, 18(12):2848-2854. Abstract from Internet address: http://pubs.acs.org/cgi-bin/abstract.cgi/cmatex/2006/18/i12/abs/cm060548q.html. Last accessed on August 4, 2008.

Bickmore, C., Galde, B., Yadav, T., and Freim, J. [assignee: Nanomaterials Research Corporation]. 1999 pat. Combustion of emulsions: a method and process for producing find powders. US Patent No. 5984997. Publication date: November 16, 1999. Internet address: http://www.freepatentsonline.com/5984997.html. Last accessed on August 19, 2008.

BizEsp. 2007. Indium tin oxide technology (ITO). Internet address: http://www.bizesp.com/uploads/ITO_FEATURE_APRIL07.pdf. Last accessed on August 4, 2008.

Blazka, M.E., Dixon, D., Haskins, E., and Rosenthal, G.J. 1994a. Pulmonary toxicity to intratracheally administered indium trichloride in Fischer 344 rats. Fundam Appl Toxicol, 22(2):231-239. Abstract from PubMed 8005375. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=8005375. Last accessed on May 21, 2009.

Blazka, M.E., Tepper, J.S., Dixon, D., Winsett, D.W., O'connor, R.W., and Luster, M.I. 1994b. Pulmonary response of Fischer 344 rats to acute nose-only inhalation of indium trichloride. Environ Res, 67(1):68-83. Abstract from PubMed 7925195. PubMed abstract Internet address:

http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=7925195. Last accessed on May 21, 2009.

Bustamante, J., Dock, L., Vahter, M., Fowler, B., and Orrenius, S. 1997. The semiconductor elements arsenic and indium induce apoptosis in rat thymocytes. Toxicology, 118(2-3):129-136. Abstract from PubMed 9129167. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=9129167. Last accessed on May 21, 2009.

Carlin, J.F., Jr. 2006. Indium. In: U.S. Geological Survey, Mineral Commodity Summaries, January 2006, pp. 82-83. Internet address: http://minerals.usgs.gov/minerals/pubs/commodity/indium/indiumcs06.pdf. Last accessed on August 18, 2008.

Ceramic Industry. 2008. Indium adds reclaim capacity with new facility. February 7, 2008. Internet address: http://www.ceramicindustry.com/Articles/Industry_News/BNP_GUID_9-5-2006_A_10000000000000253096. Last accessed on August 19, 2008.

Chagnon, M.J. 2001. Indium and indium compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology. Article online posting date: April 16, 2001 on the Wiley InterScience site (accessible only to registered users).

Chapin, R.E., Harris, M.W., Hunter, E.S., 3rd, Davis, B.J., Collins, B.J., and Lockhart, A.C. 1995. The reproductive and developmental toxicity of indium in the Swiss mouse. Fundam Appl Toxicol, 27(1):140-148. Abstract from PubMed 7589924. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=7589924. Last accessed on May 21, 2009.

ChemIDplus. Undated. Indium arsenide; RN: 1303-11-3. Internet address: http://chem.sis.nlm.nih.gov/chemidplus/ [searched by Registry Number]. Last accessed on August 19, 2008.

Chen, H.W. 2007a. Exposure and health risk of gallium, indium, and arsenic from semiconductor manufacturing industry workers. Bull Environ Contam Toxicol, 78(1):5-9.

Chen, H.W. 2007b. Exposure and health risk of gallium, indium, and arsenic from semiconductor manufacturing industry workers. Bull Environ Contam Toxicol, 78(2):123-127. [Note: This is the same publication as above for Chen (2007a); the identical article appeared twice in the same journal one month apart.]

Chonan, T., Taguchi, O., and Omae, K. 2007. Interstitial pulmonary disorders in indium-processing workers. Eur Respir J, 29(2):317-324. Internet address: http://erj.ersjournals.com/cgi/reprint/29/2/317. Last accessed on August 4, 2008.

Conner, E.A., Yamauchi, H., and Fowler, B.A. 1995. Alterations in the heme biosynthetic pathway from the III-V semiconductor metal, indium arsenide (InAs). Chem Biol Interact, 96(3):273-285. Abstract from PubMed 7538452. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=7538452. Last accessed on May 26, 2009.

Degussa AG Advanced Nanomaterials. 2006. AdNano® ITO: nanostructured indium-tin oxide. Internet address: https://www.nano-indiumtinoxide.com/webapps/adnano.nsf/download/9A069C57483742D4C125719A005003F4/$File/pi%20adnano%20ITO%2008%202006.pdf. Last accessed on August 4, 2008.

Dikensoy, O., Kervancioglu, R., Ege, I., Uysal, N., Elbek, S., and Ozkur, A. 2008. High prevalence of diffuse parenchymal lung diseases among Turkish tinners. J Occup Health, 50:208-211. Internet address: http://joh.med.uoeh-u.ac.jp/pdf/E50/E50_2_16.pdf. Last accessed on August 4, 2008.

Environment Canada. 2008. The Substances List. Search engine for chemicals and polymers. Internet address: http://www.ec.gc.ca/substances/nsb/search/eng/cp_search_e.cfm [searched by CAS Registry Number for ITO, indium oxide, and tin oxide]. Last updated on August 19, 2008. Last accessed on August 19, 2008.

Fischer, H.W., and Zimmerman, G.R. 1969. Long retention of stannic oxide. Lack of tissue reaction in laboratory animals. Arch Pathol, 88:259-264. Abstract available by searching TOXLINE for "00127596" at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE. Last accessed on August 19, 2008.

Foyol Company, Ltd. 2008. ITO targets (F-ST-2002, F-EM-1001, F-NM-1001). Internet address: http://www.fuzing.com/vli/002118742273/ITO-targets-F_ST_2002-F_EM_1001-F_NM_1001-. Last accessed on August 4, 2008.

Friz, M., and Waibel, F. 2003. Coating materials. Opt Interference Coatings, 88:105-130. Internet address: http://www.thinfilmproducts.umicore.com/library/pdf/article_coating_materials_12june03.pdf. Last accessed on August 4, 2008.

Giessen, H. 2005. Ultrafast nano-optics. Optical properties and applications of metallic photonic crystals. Internet address: http://www.pi4.uni-stuttgart.de/NeueSeite/index.html?research/photoniccrystals.html. Last updated on November 20, 2005. Last accessed on August 18, 2008.

Gordon, R.G. 2000. Criteria for choosing transparent conductors. MRS (Materials Research Society) Bulletin, August 2000, pp. 52-57. Internet address: http://lucy.mrs.org/membership/preview/aug2000bull/Gordon.pdf.

Gunay, N., Aksoy, M., Davutoglu, V., Yildirim, C., and Ege, I. 2006. Cardiac damage secondary to occupational exposure to tin vapor. Inhal Toxicol, 18(1):53-56. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16326401. Last accessed on August 19, 2008.

Hamaguchi, T., Omae, K., Takebayashi, T., Kikuchi, Y., Yoshioka, N., Nishiwaki, Y., Tanaka, A., Hirata, M., Taguchi, O., and Chonan, T. 2008. Exposure to hardly soluble indium compounds in ITO production and recycling plants is new risk for interstitial lung damage. Occup Environ Med, 65:51-55. Internet address: http://www.bvsde.paho.org/bvsacd/cd67/hardly.pdf. Last accessed on August 4, 2008.

Homma, T., Ueno, T., Sekizawa, K., Tanaka, A., and Hirata, M. 2003. Interstitial pneumonia developed in a worker dealing with particles containing indium-tin oxide. J Occup Health, 45(3):137-139. Internet address: http://www.jstage.jst.go.jp/article/joh/45/3/137/_pdf. Last accessed on August 19, 2008.

Homma, S., Miyamoto, A., Sakamoto, S., Kishi, K., Motoi, N., and Yoshimura, K. 2005. Pulmonary fibrosis in an individual occupationally exposed to inhaled indium-tin oxide. Eur Respir J, 25(1):200-204. Internet address: http://erj.ersjournals.com/cgi/reprint/25/1/200. Last accessed on August 19, 2008.

HSDB (Hazardous Substances Data Bank). 2002. Indium compounds. HSDB No. 6995. Profile last updated on October 11, 2002. Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel++@na+indium+compounds. Last accessed on August 19, 2008.

HSDB. 2005a. Tin oxide (CASRN: 18282-10-5). HSDB No. 5064. Profile last updated on June 23, 2005. Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+18282-10-5. Last accessed on August 19, 2008.

HSDB. 2005b. Indium trichloride (CASRN: 10025-82-8). HSDB No. 6973. Profile last updated on June 23, 2005. Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+10025-82-8. Last accessed on May 20, 2009.

HSDB. 2005c. Indium phosphide (CASRN: 22398-80-7). HSDB No. 6935. Profile last updated on June 23, 2005. Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+22398-80-7. Last accessed on August 19, 2008.

Indium Corporation. Undated. Product data sheet: Indium-tin oxide (ITO). Internet address: http://www.indium.com/documents/pds/97550.pdf. Last accessed on August 4, 2008.

IPCS (International Programme for Chemical Safety). 2005. Concise International Chemical Assessment Document (CICAD) 65. Tin and Inorganic Tin Compounds. World Health Organization, Geneva, Switzerland. Internet address: http://www.inchem.org/documents/cicads/cicads/cicad65.htm. Last accessed on August 19, 2008.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). 1982. 552. Tin and Stannous Chloride. WHO Food Additives Series 17. World Health Organization, Geneva, Switzerland. Internet address: http://www.inchem.org/documents/jecfa/jecmono/v17je32.htm. Last accessed on August 19, 2008.

Jorgenson, J.D., and George, M.W. 2005. Mineral Commodity Profile: Indium. Open-File Report 2004-1300. U.S. Department of the Interior, U.S. Geological Survey, Reston, VA. Internet address: http://pubs.usgs.gov/of/2004/1300/2004-1300.pdf. Last accessed on August 19, 2008.

Kim, S.-M., Seo, K.-H., Lee, J.-H., Kim, J.-J., Lee, H. Y., and Lee, J.-S. 2006. Preparation and sintering of nanocrystalline ITO powders with different SnO_2 content. J Eur Ceram Soc, 26:73-80. Internet address: http://yu.ac.kr/~hyulee/papers/ITO-Sn.pdf. Last accessed on August 19, 2008.

King County Solid Waste Division, DNRP (Department of Natural Resources and Parks). 2008. Literature review: Flat panel displays: end of life management report. Final report. King County Solid Waste Division, Seattle, WA, 134 pp. Internet address: http://www.metrokc.gov/dnrp/swd/takeitback/electronics/documents/FPDReport.pdf. Last accessed on August 4, 2008.

Labedzka, M., Gulyas, H., Schmidt, N., and Gercken, G. 1989. Toxicity of metallic ions and oxides to rabbit alveolar macrophages. Environ Res, 48(2):255-274. Abstract from PubMed 2538328. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=2538328. Last accessed on August 19, 2008.

Laloy, J., Muller, J., and Lison, D. 2007. Experimental assessment of the pulmonary toxicity of ITO particles. Report for Umicore. Submitted in accordance with Section 8(e) of the TSCA to Office of Pollution Prevention and Toxics, U.S. EPA, Washington, DC. Internet address: http://www.epa.gov/oppt/tsca8e/pubs/8ehq/2007/jun07/8ehq_0607_16847b_89070000363.pdf. Last accessed on August 4, 2008.

Lee, J.-S., and Choi, S.-C. 2005. Solvent effect on synthesis of indium tin oxide nano-powders by a solvothermal process. J Eur Ceram Soc, 25(14):3307-3314. Abstract from Internet address: http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TX0-4DTKY19-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=997cfcfa20d6cad188042e585e19bc08. Last accessed on August 19, 2008.

Liao, Y.H., Yu, H.S., Ho, C.K., Wu, M.T., Yang, C.Y., Chen, J.R., and Chang, C.C. 2004. Biological monitoring of exposures to aluminium, gallium, indium, arsenic, and antimony in optoelectronic industry workers. J Occup Environ Med, 46(9):931-936. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15354058. Last accessed on August 19, 2008.

Liao, Y.H., Hwang, L.C., Kao, J.S., Yiin, S.J., Lin, S.F., Lin, C.H., Lin, Y.C., and Aw, T.C. 2006. Lipid peroxidation in workers exposed to aluminium, gallium, indium, arsenic, and antimony in the optoelectronic industry. J Occup Environ Med, 48(8):789-793. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16902371. Last accessed on August 19, 2008.

Lison, D., Laloy, J, Corazzari, I., Muller, J., Rabolli, V., Panin, N., Huaux, F., Fenoglio, I., and Fubini, B. 2009. Sintered indium-tin-oxide (ITO) particles: a new pneumotoxic entity. Toxicol Sci, 108(2):472-481. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=19176593. Last accessed on May 26, 2009.

Lo, C.-F., Turn, J., Strauss, D.P. [assignee: Sony Corporation (Tokyo, Japan) and Materials Research Corporation (Gilbert, AZ)]. 1997 pat. Method for making metal oxide sputtering targets (barrier powder envelope). US Patent No. 5,656,216. Publication date: August 12, 1997. Internet address: http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN%2F5656216. Last accessed on August 4, 2008.

Miyaki, K., Hosoda, K., Hirata, M., Tanaka, A., Nishiwaki, Y., Takebayashi, T., Inoue, N., and Omae, K. 2003. Biological monitoring of indium by means of graphite furnace atomic absorption spectrophotometry in workers exposed to particles of indium compounds. J Occup Health, 45(4):228-230. Internet address: http://www.jstage.jst.go.jp/article/joh/45/4/228/_pdf. Last accessed on August 19, 2008.

Monteiles, J. (Editor, Criteria Group for Occupational Standards). 2005. Consensus report for tin and inorganic tin compounds (October 22, 2003). In: Scientific Basis for Swedish Occupational Standards XXV. No. 2005:7. Translated by Frances Van Sant. [Arbet Och Hälsa 7:1-15.] National Institute for Working Life, Stockholm, Sweden, pp. 1-15. Internet address: https://gupea.ub.gu.se/dspace/bitstream/2077/4352/1/ah2005_07.pdf. Last accessed on August 19, 2008.

Morrow, P.E., Gibb, F.R., Cloutier, R., Casarett, L.J., and Scott, J.K. 1957. Fate of indium sesquioxide and indium114 trichloride hydrolysate following inhalation in rats. U.S. Atomic Energy Commission. UR-508. October 9, 1957. 33 pp. Abstract from Energy Citations Database OSTI ID: 4345461. Internet address: http://www.osti.gov/energycitations/product.biblio.jsp?osti_id=4345461&query_id=0. Last accessed on August 19, 2008.

Morvai, V., Ungvary, G., and Szakmary, E. 2001. Hemodynamic effect of indium chloride in pregnant rats. J Toxicol Environ Health A, 62(5):397-407. Abstract from PubMed 11261901. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11261901. Last accessed on May 22, 2009.

Nakajima, M., Kobayashi, Y., Usami, M., and Ohno, Y. 1998 abstr. Teratogenic effects of indium by oral or intravenous administration in rats. Teratology, 57(3):19A. Abstract from DART/TER/98000838. Internet address: http://toxnet.nlm.nih.gov/ [searched for "indium trichloride" on DART database]. Last accessed on May 22, 2009.

Nakajima, M., Takahashi, H., Sasaki, M., Kobayashi, Y., Awano, T., Irie, D., Sakemi, K., Ohno, Y., and Usami, M. 1998. Developmental toxicity of indium chloride by intravenous or oral administration in rats. Teratog Carcinog Mutagen, 18(5):231-238. Abstract from PubMed 9876012. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=9876012. Last accessed on May 26, 2009.

Nakajima, M., Takahashi, H., Sasaki, M., Kobayashi, Y., Ohno, Y., and Usami, M. 2000. Comparative developmental toxicity study of indium in rats and mice. Teratog Carcinog Mutagen, 20(4):219-227. Abstract from PubMed 10910472. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=10910472. Last accessed on May 26, 2009.

Nakajima, M., Takahashi, H., Nakazawa, K., and Usami, M. 2007. Fetal cartilage malformation by intravenous administration of indium trichloride to pregnant rats. Reprod Toxicol, 24(3-4):409-413. Abstract from PubMed 17646080. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=17646080. Last accessed on May 8, 2009.

Nakajima, M., Mitsunaga, K., Nakazawa, K., and Usami, M. 2008. In vivo/in vitro study in rat embryos on indium-caused tail malformations. Reprod Toxicol, 25(4):426-432. Abstract from PubMed 18547785. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=18547785. Last accessed on May 22, 2009.

Nanophase Technologies. 2008. Nanoparticles: NanoTek® Indium Tin Oxide. Product Code #0600. Internet address: http://www.nanophase.com/catalog/item.asp?ITEM_ID=35&DEPARTMENT_ID=38. Last accessed on August 19, 2008.

Nettleton, J.S., Lawson, R.S., Prescott, M.C., and Morris, I.D. 2004. Uptake, localization, and dosimetry of 111In and 201Tl in human testes. J Nucl Med, 45(1):138-146. Internet address: http://jnm.snmjournals.org/cgi/reprint/45/1/138. Last accessed on May 26, 2009.

NIOSH (National Instittue for Occupational Safety and Health). 2005. NIOSH pocket guide to chemical hazards: Indium. NIOSH Publication 2005-149. Internet address: http://www.cdc.gov/NIOSH/npg/npgd0341.html. Last accessed on May 20, 2009.

Nogami, H., Shimoda, T., Shoji, S., and Nishima, S. 2008. Pulmonary disorders in indium-processing workers (Japanese). Nihon Kokyuki Gakkai Zasshi, 46(1):60-64. Abstract from PubMed 16280313. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16280313. Last accessed on May 8, 2009.

NTP (National Toxicology Program). 2001. Abstract for TR-499 – Indium Phosphide. [TR-499: Toxicology and Carcinogenesis Studies of Indium Phosphide (CAS No. 22398-80-7) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies)] Report date: July 2001. Internet address: http://ntp.niehs.nih.gov/index.cfm?objectid=070B0BF9-AFC9-B97A-E6B0DF1E4DC577F6. Last accessed on August 19, 2008.

Okabe, K., Nishimura, T., Sato, S., Eshima, K., Toishi, K., and Nagata, C. [assignee: Dowa Mining Co., Ltd. (Tokyo, Japan)]. 2000 pat. Starting powders for ITO production, ITO sinters and processes for producing such starting powders and ITO sinters. US Patent No. 6099985. Publication date: August 8, 2000. Internet address: http://www.freepatentsonline.com/6099982.html. Last accessed on August 4, 2008.

Omura, M., Yamazaki, K., Tanaka, A., Hirata, M., Makita, Y., and Inoue, N. 2000. Changes in the testicular damage caused by indium arsenide and indium phosphide in hamsters during two years after intratracheal instillation. J Occup Health, 42:196-204. Internet address: http://joh.med.uoeh-u.ac.jp/pdf/E42/E42_4_06.pdf. Last accessed on August 19, 2008.

Omura, M., Tanaka, A., Hirata, M., Inoue, N., Ueno, T., Homma, T., and Serizawa, K. 2002. Testicular toxicity evaluation of indium-tin oxide. J Occup Health, 44(2):105-102. Internet address: http://joh.med.uoeh-u.ac.jp/pdf/E44/E44_2_08.pdf. Last accessed on August 19, 2008.

PGO (präzisions glas & optic). Undated. ITO-Coatings on high quality glass substrates. Internet address: http://www.pgo-online.com/intl/katalog/ito.html. Last accessed on August 19, 2008.

Phipps, G., Mikolajczak, C., and Guckes, T. 2007. Indium and gallium supply sustainability. September 2007 update. Internet address: http://www.indium.com/_dynamo/download.php?docid=552. Last accessed on August 4, 2008.

Psuja, P., Hreniak, D., and Strek, W. 2009. Synthesis and characterization of indium-tin-oxide nanostructures. J Phys Conf Ser, 146:012033 (10 pages). Internet address: http://www.iop.org/EJ/article/1742-6596/146/1/012033/jpconf9_146_012033.pdf?request-id=f95a1946-d236-4377-96c4-35458ca19627. Last accessed on May 26, 2009.

PubChem. Undated. Compound/Substance Summary for

- Indium tin oxide [substance summary]. Internet address: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?sid=3764630&version=2.
- Indium trichloride [compound summary]. Internet address: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=24812
- Indium phosphide [compound summary]. Internet address: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?db=pccompound&term=31170.
- Indium arsenide [compound summary]. Internet address: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?db=pccompound&term=91500.

Last accessed on August 19, 2008, except May 20, 2009 for indium trichloride record.

Reade Advanced Materials. 2006. Indium-Tin Oxide Powder. Internet address: http://www.reade.com/index.php?option=com_content&task=view&id=262&Itemid=10. Last accessed on August 19, 2008.

Registry. 2006. RN 50926-11-9. Database available from the American Chemical Society on STN. Record entered STN on November 16, 1984.

RTECS (Registry for Toxic Effects of Chemical Substances). 2008. RTECS No. XQ4000000. Internet address: http://www.cdc.gov/niosh/rtecs/xq3d0900.html. Last accessed on August 19, 2008.

Rushe, N., Ball, M., Carroll, W.M., Healy, S., McManus, J., and Cunningham, D. 2005. Cytocompatibility of novel tin oxide thin films. J Mater Sci Mater Med, 16(3):247-252. Abstract from PubMed 15744616. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=15744616. Last accessed on May 8, 2009.

Schlott, M., Dauth, W., and Kutzner, M. [assignee: Leybold Materials GmbH]. 1997 pat. Process for the recycling of spent indium oxide-tin oxide sputtering targets. US Patent No. 5660599. Issue date: August 26, 1997. Internet address: http://www.patentstorm.us/patents/5660599/fulltext.html. Last accessed on August 4, 2008.

Smith, I.C., Carson, B.L., and Hoffmeister, F. 1978. Trace Metals in the Environment. Volume 5—Indium: An Appraisal of Environmental Exposure. Ann Arbor Science Publishers, Ann Arbor, MI. [Without the index, this volume is equivalent to a report prepared for the National Institute for Environmental Health Sciences in 1978 under Midwest Research Institute contract N01-ES-2-2090, "Appraisal of Environmental Exposure to Heavy Metals."]

Swarts, N. [Indium Corporation of America]. 2006. Material safety data sheet (MSDS): Indium tin oxide. MSDS No. MSDS-IB011. Record last revised on May 3, 2006. Internet address: http://www.indium.com/documents/msds/IB011.pdf. Last accessed on August 19, 2008.

Taguchi, O., and Chonan, T. 2006. Three cases of indium lung (Japanese). Nihon Kokyuki Gakkai Zasshi, 44(7):532-536. Abstract from PubMed 16886812 . PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16886812. Last accessed on May 8, 2009.

Tanaka, A., Hirata, M., Omura, M., Inoue, N., Ueno, T., Homma, T., and Kiyohisa, S. 2002. Pulmonary toxicity of indium-tin oxide and indium phosphide after intratracheal instillations into the lung of hamsters. J Occup Health, 44(2):99-102. Internet address: http://joh.med.uoeh-u.ac.jp/pdf/E44/E44_2_06.pdf. Last accessed on August 19, 2008.

Tanaka, A., Hirata, M., and Omura, M. 2003. Pulmonary squamous cyst induced by exposure to indium arsenide in hamsters. J Occup Health, 45(6):405-407. Internet address: http://www.jstage.jst.go.jp/article/joh/45/6/405/_pdf. Last accessed on August 19, 2008.

Tolcin, A.C. 2008. Indium. In: 2006 Minerals Yearbook. U.S. Geological Survey, U.S. Department of the Interior. Internet address: http://minerals.usgs.gov/minerals/pubs/commodity/indium/myb1-2006-indiu.pdf. Last accessed on August 4, 2008.

U.S. EPA (U.S. Environmental Protection Agency). 2004. Health and safety data reporting; addition of certain chemicals. Fed Regist, 69(86):24517-24524. Internet address: http://www.epa.gov/EPA-TOX/2004/May/Day-04/t9875.htm. Last accessed on August 19, 2008.

U.S. EPA. 2005. Fifty-sixth report of the TSCA Interagency Testing Committee to the Administrator of the Environmental Protection Agency; receipt of report and request for comments; notice. Fed Regist, 70(204):61520-61541. Internet address: http://www.epa.gov/fedrgstr/EPA-TOX/2005/October/Day-24/t21197.pdf. Last accessed on August 19, 2008.

U.S. EPA. 2006. Fifty-eighth report of the TSCA Interagency Testing Committee to the Administrator of the Environmental Protection Agency; receipt of report and request for comments. Fed Regist, 71(132):39187-39202. Internet address: http://www.epa.gov/EPA-TOX/2006/July/Day-11/t6126.htm. Last accessed on September 8, 2008.

Umicore. 2005. Technical data: Indium tin oxide (ITO) sputtering target. Internet address: http://www.thinfilmproducts.umicore.com/pdf/indium_tin_oxide_ITO.pdf. Last accessed on August 19, 2008.

Ungváry, G., Szakmáry, E., Tátrai, E., Hudák, A., Náray, M., and Morvai, V. 2000. Embryotoxic and teratogenic effects of indium chloride in rats and rabbits. J Toxicol Environ Health A, 59(1):27-42. Abstract from PubMed 10681097. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=10681097. Last accessed on May 26, 2009.

Ungváry, G., Tátrai, E., Szakmáry, E., and Náray, M. 2001. The effect of prenatal indium chloride exposure on chondrogenic ossification. J Toxicol Environ Health A, 62(5):387-396. Abstract from PubMed 11261900. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11261900. Last accessed on May 8, 2009.

Van Hulle, M., De Cremer, K., Cornelis, R., and Lameire, N. 2001. In vivo distribution and speciation of [114mIn]InCl3 in the Wistar rat. J Environ Monit, 3(1):86-90. Abstract from PubMed 11253025. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11253025. Last accessed on May 26, 2009.

Wang, L. 1988. Effect of antimonous oxide, aluminum oxide, and stannic oxide dust on pulmonary alveolar macrophages *in vitro* and *in vivo* (Chinese). Zhongua Laodong Weisheng Zhiyebing Zazhi, 6(5):277-280. Abstract from CAPLUS 1990:71928.

Wang, F.S., Liu, L.F., Chen, N.M., and Li, Y.R. 1994. A study on cellular reactions and fibrogenic effects of mineral dusts. Biomed Environ Sci, 7(2):116-121. Abstract from PubMed 7946006. PubMed abstract Internet

address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=7946006. Last accessed on May 8, 2009.

Xu, H., Zhu, G., and Zhou, H. 2005. Preparation of monodispersed Tin-Doped Indium Oxide Powders by Hydrotermal Method. J. Am. Ceram. Soc. 88(4):986-988. Cited by Psuja et al. (2009).

Zhang, J., Au, K.H., and Chang, S.Y. 2004. Investigation of sol-gel derived indium tin oxide thin films with poly(ethylene glycol) as an additive. J Ceram Proc Res, 5(3):208-213. Internet address: http://jcpr.kbs-lab.co.kr/english/journal/JCPR/vol5num3/208-213.pdf. Last accessed on August 4, 2008.

Zhou, J. 2005 thesis. Indium tin oxide (ITO) deposition, patterning, and Schottky contact fabrication. Department of Microelectronic Engineering, Rochester Institute of Technology, Rochester, NY, 89 pp. Internet address: http://www.rit.edu/kgcoe/ue/thesisguidelinespages/2006_Jianming_Zhou.pdf. Last accessed on August 4, 2008.

Acknowledgements

Support to the National Toxicology Program for the preparation of Chemical Information Profile for Indium Tin Oxide was provided by Integrated Laboratory Systems, Inc., through NIEHS Contract Nos. N01-ES-35515 (2006-2008) and HHSN273200800008C (2009). Contributors included: Scott A. Masten, Ph.D. (Project Officer, NIEHS); Marcus A. Jackson, B.A. (Principal Investigator, ILS, Inc.); Bonnie L. Carson, M.S. (ILS, Inc.); Claudine A. Gregorio, M.A. (ILS, Inc.); Nathanael P. Kibler, B.A. (ILS, Inc.); and Sherry D. Blue, A.A. (ILS, Inc.).

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, ESBIOBASE, 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://ww.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

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
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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.

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2009 Update:  STN International database files MEDLINE, AGRICOLA, CABA, IPA,
BIOSIS, TOXCENTER, FSTA, FROSTI, EMBASE, ESBIOBASE, 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 X370OTHER09/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).

References

Armistead, P.M., and Thorp, H.H. 2000. Modification of indium tin oxide electrodes with nucleic acids: detection of attomole quantities of immobilized DNA by electrocatalysis. Anal Chem, 72(16):3764-3670. Abstract from PubMed 10959961. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=10959961. Last accessed on May 4, 2009.

Beach, R.D., Conlan, R.W. Godwin, M.C., and Moussy, F. 2005. Towards a miniature implantable in vivo telemetry monitoring system dynamically configurable as a potentiostat or galvanostat for two- and three-electrode biosensors. Instrumentation and Measurement, IEEE Transactions 54(1):61-72. Abstract at Internet address: http://ieeexplore.ieee.org/xpl/absprintf.jsp?arnumber=1381799&page=FREE. Last accessed on June 1, 2006.

Burnett, P., Robertson, J.K., and Zivin, R.A. [assignee: Standard Mems, Inc.]. 2004 pat. Electrophysiology assay methods. World Patent number WO 2004012585. February 12, 2004. PCT Int Appl, 52 pp. Abstract from TOXCENTER 2004:41480 (also CAPLUS 2004:120658).

Chakrabarty, K., and Su, F. 2005. Design automation challenges for microfluidics-based biochips. Paper presented at the Symposium on Design, Test, Integration and Packaging [DTIP] of MEMS/MOEMS at Montreux, Switzerland, June 1-3, 2005. TIMA Labs/DTIP. TIMA Laboratory [Techniques of Informatics and Microelectronics for Computer Architecture], Grenoble, France. Internet address: http://www.ee.duke.edu/~krish/cr1113.pdf. Last accessed on June 1, 2006.

Eggins, B.R., Byrne, J.A., Dunlop, P.S.M., and Davidson, A. 1999. TiO2 particulate films on indium tin oxide coated glass and their use for water treatment. Topical Issues Glass, 3(Photons, Glasses and Coatings):57-62. Abstract from TOXCENTER 2000:154108 (also CAPLUS 2000:370741).

Fukuba, T., Naganuma, T., and Fujii, T. 2003. Microfabricated flow-through PCR device for in situ gene analysis in extreme environments. In: Proceedings of the 7th International Conference on Miniaturized Chemical and Biochemical Analysis Systems, Squaw Valley, California, October 5-9, 2003, pp. 725-728. Internet address: http://www.chem.ualberta.ca/~microtas/Volume1/180-220.pdf. Last accessed on June 1, 2006.

Gross, G.W., Rhoades, B.K., Reust, D.L., and Schwalm, F.U. 1993. Stimulation of monolayer networks in culture through thin-film indium-tin oxide recording electrodes. J Neurosci Methods, 50(2):131-143. Abstract from PubMed 8107494. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=8107494. Last accessed on May 4, 2009.

Lewis, N.S. [assignee: California Institute of Technology]. 2000 pat. Method and device to analyze components of fluids in clinical, environmental, and food samples using sensors with conductive elements and chemically sensitive resistors. World Patent number WO 20000026638. May 11, 2000. PCT Int Appl, 70 pp. Abstract from TOXCENTER 2000:147256 (also from CAPLUS 2000:314908).

Lim, T.-K., Murakami, T., Tsuboi, M., Yamashita, K., and Matsunaga, T. 2003. Preparation of a colored conductive paint electrode for electrochemical inactivation of marine bacteria. Biotechnol Bioeng, 81(3):299-304. Abstract from PubMed 12474252. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=12474252. Last accessed on May 4, 2009.

Mitsubayashi, , K., Tatsuro, E., Satoshi, S., and Karube, I. 2001. Optical-transparent oxygen sensor with a thinner membrane structure. Anal Sci, 17(Supplement):i773-i776. Internet address: http://wwwsoc.nii.ac.jp/jsac/analsci/ICAS2001/pdfs/0700/0773_4h08n.pdf. Last accessed on June 1, 2006.

Pancrazio, J.J., Whelan, J.P., Borkholder, D.A., Ma, W., and Stenger, D.A. 1999. Development and application of cell-based biosensors. Ann Biomed Eng, 27(6):697-711. Abstract from Pubmed 10625143. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=10625143. Last accessed on May 4, 2009.

Raptis, L., and Firth, K.L. 1990. Electroporation of adherent cells in situ. DNA Cell Biol, 9(8):615-621. Abstract from PubMed 2271121. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=2271121. Last accessed on May 4, 2009.

Selvakumaran, J., Hughes, M.P., Keddie, J.L., and Ewins, D.J. 2002. Assessing biocompatibility of materials for implantable microelectrodes using cytotoxicity and protein adsorption studies. Microtechnologies in Medicine and Biology, 2nd Annual International IEEE-EMB Special Topics Conference, Madison, WI, May 2-4, 2002, pp. 261-264. Abstract at Internet address: http://ieeexplore.ieee.org/xpl/absprintf.jsp?arnumber=1002326&page=FREE. Last accessed on June 1, 2006.

Tang, C.S., Dusseiller, M., Makohliso, S., Heuschkel, M., Sharma, S., Keller, B., and Voros, J. 2006. Dynamic, electronically switchablesurfaces for membrant protein microarrays. Anal Chem, 78(3):711-717. Abstract from PubMed 16448043. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16448043. Last accessed on May 4, 2009.

Tomai, E., Klein, S., Firth, K., and Raptis, L. 2000. Growth on indium-tin-oxide-coated glass enhances 32P-phosphate uptake and protein labelling of adherent cells. Prep Biochem Biotechnol, 30(4):313-320. Abstract from PubMed 11065276. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=11065276. Last accessed on May 4, 2009.

Yamauchi, F., Kato, K., and Iwata, H. 2005. Layer-by-layer assembly of poly(ethyleneimine) and plasmid DNA onto transparent indium-tin oxide electrodes for temporally and spatially specific gene transfer. Langmuir, 21(18):8360-8367. Abstract from PubMed 16114943. PubMed abstract Internet address: http://www.ncbi.nlm.nih.gov/sites/entrez?orig_db=PubMed&db=pubmed&cmd=Search&TransSchema=title&term=16114943. Last accessed on May 4, 2009.

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