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Review

The toxicology of indium tin oxide

Ernst M. Bomhard*

REACh ChemConsult GmbH, Strehlener Str. 14, D-01069 Dresden, Germany

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ABSTRACT

Indium tin oxide (ITO) is a technologically important semiconductor. An increasing number of cases of severe lung effects (characterized by pulmonary alveolar proteinosis and/or interstitial fibrosis) in ITO-exposed workers warrants a review of the toxicological hazards. Short- and long-term inhalation studies in rats and mice revealed persistent alveolar proteinosis, inflammation and fibrosis in the lungs down to concentrations as low as 0.01 mg/m^3. In rats, the incidences of bronchiolo-alveolar adenomas and carcinomas were significantly increased at all concentrations. In mice, ITO was not carcinogenic. A few bronchiolo-alveolar adenomas occurring after repeated intratracheal instillation of ITO to hamsters have to be interpreted as treatment-related. In vitro and in vivo studies on the formation of reactive oxygen species suggest epigenetic effects as cause of the lung tumor development. Repeated intratracheal instillation of ITO to hamsters slightly affected the male sexual organs, which might be interpreted as a secondary effect of the lung damage. Epidemiological and medical surveillance studies, serum/blood indium levels in workers as well as data on the exposure to airborne indium concentrations indicate a need for measures to reduce exposure at ITO workplaces.

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* Corresponding author.
E-mail address: bomhard@reach-chemconsult.com

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1. Introduction

ITO is a heavily-doped n-type semiconductor with a large bandgap of around 4 eV widely used in optical devices due to high electrical conductivity and high transparency at visible light wavelengths (Kim et al., 1999). It has the generic CAS No. 50926-11-9. It typically consists of approximately 90% indium oxide (In_2O_3) and 10% tin oxide (SnO) by weight and can be sintered or unsintered. In thin layers, ITO is transparent and colorless. The specific gravity ranges from 6.65–7.34 g/cm^3; it sublimes at 982 °C and the melting point is 1910 °C. Tin substitutes for indium in ITO crystals form 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. Typical ITO films are 1500–3500 Ångstroms thick. 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 production generally starts with indium metal, which is used to make indium oxide powder. Indium oxide and tin oxide powders are then blended together, 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. The sintered tiles, or targets, are ground and cut to the customer's specifications for sputtering (Cummings et al., 2013; Hines et al., 2013; NTP, 2009).

The following Fig. 1 (taken from MHLW, 2010) illustrates the way ITO is synthesized and used.

ITO has a broad range of applications such 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 (NTP, 2009).

Occupational exposure to particles generated during ITO production has increased in recent years due to the rising demand for consumer electronics. Thus, there is a need to assess hazards and risks of ITO, the more because in recent years an increasing number of lung diseases after occupational exposure has been reported in the literature essentially from workers in Korea and Japan, some of which were fatal.

The toxicology of ITO has not yet been comprehensively reviewed. In the following, the available data are therefore compiled and critically reviewed.

The journal databases consulted in the course of the review were PubMed, Google and the reference lists of the papers found. The review covers the years 1990–2016 (first months).

2. Acute toxicity

Studies on the acute toxicity of ITO by the oral, dermal or inhalation route using standard test guidelines are not available. An oral LD50 value of greater than 10 g/kg in rats is mentioned by MHLW (2010), but no reference is provided.

2.1. Special acute studies on lung toxicity

Female Wistar rats were administered a single dose of 2–20 mg UITO particles (median mass diameter 7 μm[1]) per rat by pharyngeal aspiration. Inflammatory response (by analyzing bronchoalveolar lavage fluid (BALF) and histology) and fibrotic response (by measuring the lung hydroxyproline and soluble collagen content) were assessed 3, 15 and 60 days after particle administration.

BALF parameters and histopathology indicated a protracted inflammation but there was no indication of a fibrotic reaction in the lung. The damage was essentially characterized by an alveolitis accompanied with a thickening of the alveolar wall and the presence of macrophages, lymphocytes and polymorphonucleated neutrophils (Lison et al., 2009).

Male Sprague–Dawley rats were intratracheally instilled with single doses of 1.0 and 5.0 mg sintered ITO (SITO; mean aerodynamic diameter 1.2 ± 0.8 μm) per rat. After 1, 7 and 90 days, BALF examination gave clear indications of pulmonary inflammation. Histopathology (after 90 days) revealed, in addition, pulmonary alveolar proteinosis (PAP) and fibrosis (Badding et al., 2016).

B6C3F1 mice were administered a single dose of 0.5 or 1 mg SITO/kg BW by oropharyngeal aspiration (particle diameter ≈ 1.7 μm; vehicle phosphate-buffered saline). On days 14 and 28 after dosing, BALF and pleural lavage fluid (PLF) were collected. None of the parameters measured in the BALF (lactate dehydrogenase activity, total protein, total cells, macrophages, polymorphonuclear leukocytes), as well as the number of cells in the PLF was significantly increased compared with vehicle (saline) controls (Gwinn et al., 2015). Histopathology was not performed.

3. Local effects on skin and mucous membranes

Studies on local effects on skin and mucous membranes of ITO using standard test guidelines are not available.

In a material safety data sheet on ITO of the Indium Corporation of America the following hazard statements are given: "causes skin irritation, causes serious eye irritation and may cause respiratory irritation" (Swarts, 2015). No references are provided for these statements.

Female BALB/c mice were exposed on the breached skin of each ear to 25 ml of vehicle (DMSO) or 10% UITO (particle size < 50 nm) for three consecutive days. Exposure produced no changes in body

[1] All data on particle dimensions are given as reported.